National Institute for Health and Care Excellence

Draft for consultation

Barrett's oesophagus

2.1 Evidence review for endoscopic surveillance

NICE guideline <number>

Evidence reviews underpinning recommendations 1.3.1 – 1.3.4 in the NICE guideline

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Draft for consultation

These evidence reviews were developed by Guideline Development Team NGC

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1 Endoscopic Surveillance

1.1 Review question

For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of endoscopic surveillance using white light endoscopy?

1.1.1 Introduction

It is recommended that patients with Barrett's Oesophagus undergo regular surveillance endoscopies with mapping biopsies. The aim of surveillance is to detect dysplastic cell change, and progression to oesophageal adenocarcinoma, at the earliest possible opportunity. This allows for timely intervention, leading ultimately to improved survival rates for patients. The benefits of endoscopic surveillance must be balanced with the risks of the procedure to each individual and discussions around the recommended frequency of surveillance must also include a consideration of its clinical and cost effectiveness.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults, 18 years and over, with Barrett's oesophagus (with or without dysplasia) Exclusion: Those with disease that does not fit within definition of Barrett's
Intervention	• white light endoscopy
Comparison	• no surveillance (disease extent doesn't meet definition; benefit of surveillance isn't appropriate)
Outcomes	• Mortality • Health related quality of life (validated scores) • Progression of dysplasia • Progression to cancer and stage • Adverse events (such as sedation related, bleeding, pain, perforation) Time points: beyond 1 year of follow up (minimum) up to longest follow up period
Study design	RCTs, or observational if no RCTs

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

We initially searched for RCTs, comparing white light endoscopy surveillance to no endoscopy surveillance, but no RCTs were found. We therefore searched for observational studies, and seven eligible observational studies were included in the review. [2, 4, 13, 17, 18, 20, 21] These are summarised in Table 2 below, and evidence from these studies is summarised in the clinical evidence summary below (Table 3).

None of the studies specifically mentioned 'white light' endoscopy, merely referring to 'endoscopy' instead. These studies were not excluded, however, because white light endoscopy is the standard form of endoscopy, and the committee agreed it is most likely that the studies were evaluating the correct modality. For brevity we have used the term surveillance in this review to mean endoscopic surveillance.

The main limitation of the studies was the high risk of bias inherent in their observational design. Rigorous statistical adjustment[4, 21], or limited statistical adjustment combined with matching[2] was used by three studies and this has been judged to have partially reduced the risk of selection bias. The remaining studies [13, 17, 18, 20] failed to adjust for any potential confounding and are therefore at very high risk of selection bias. The results from these four studies should thus be interpreted with caution. The decision was made before analysis that adjusted and non-adjusted studies should not be pooled because of the likelihood that their effects would differ, and so separate meta-analyses have been made for each. By necessity, we have presented the measures of effect that were calculated in the adjusted analyses, but for studies where adjustment was not carried out we have presented results as risk ratios, in order to enable the calculation of absolute risk differences.

Two meta-analyses showed very serious heterogeneity. However, it was not possible to use the pre-hoc sub-grouping strategy (related to the adequacy of endoscopy) to attempt to resolve the heterogeneity. In one case the analysis only involved one study in one of the sub-groups, which precludes use of sub-grouping because this will always spuriously 'resolve' heterogeneity in that sub-group even when there is no association between the sub-grouping variable and the outcome effect size. In the other case, sub-grouping simply failed to resolve the inconsistency. Both analyses have therefore been re-analysed with a random effects model to allow for the fact that in each meta-analysis the studies are probably not estimating from a common population mean.

Important abbreviations used in this review are OAC (oesophageal adenocarcinoma), and Barrett's (Barrett's Oesophagus).

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 I.

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	Sub-group (adequate surveillance or non-adequate surveillance)	Comments
Corley, 2013[2]	Surveillance endoscopy: any esophagogastroduodenoscopy performed principally for cancer surveillance of a previously documented Barrett's oesophagus, not for symptoms. (N=82) Vs No surveillance (N=57)	Cases: People diagnosed with oesophageal or gastroesophageal junction adenocarcinoma; with a Barrett's oesophagus diagnosis 6 months or more before their cancer diagnosis; who subsequently died of oesophageal/gastroesophageal junction adenocarcinoma or its complications(N=38). Controls: had a diagnosis of Barrett's oesophagus who did not die of oesophageal or gastroesophageal junction adenocarcinoma through the end of the follow-up evaluation(N=101). Controls were matched to cases by age at Barrett's oesophagus diagnosis, year of Barrett's	Mortality from OAC At 3-year follow-up	Not possible to define as adequacy of surveillance not reported	Case control study The cases and matched controls defined the outcome of oesophageal adenocarcinoma (OAC) mortality, and the association with prior surveillance was investigated with conditional logistic regression. The logistic regression analysis only adjusted for dysplasia status but the controls were already fairly well-matched to the cases on the basis of a number of plausible potential confounders (see population column) so to some extent quite reasonable attempts were made to reduce selection bias.

Study	Intervention and comparison	Population	Outcomes	Sub-group (adequate surveillance or non-adequate surveillance)	Comments
		oesophagus diagnosis, medical centre of Barrett's oesophagus diagnosis, sex, and race. Mean age at index date: surveillance group= 73.5 (8.2); no surveillance group=73.8 (8.1) USA			The reasons for the comparator group not having surveillance was not explained.
El-Serag, 2016[4]	Barrett's Surveillance: included patients who received surveillance endoscopy for non-dysplastic Barrett's, or surveillance endoscopy for Barrett's with dysplasia initially detected as a result of Barrett's surveillance. Vs Comparator: Patients whose OAC was initially detected on diagnostic endoscopy, screening endoscopy, unknown indication for endoscopy or surveillance endoscopy for dysplasia originally detected in non-Barrett's surveillance endoscopy	Patients with Barrett's and OAC who were >18 years of age at Barrett's index date and had at least 1 year of follow-up after the index Barrett's endoscopy as well as before their last VA visit or date of oesophageal cancer(N=424). Mean age (SD): 61.9 (9.9) USA	Mortality from OAC All-cause mortality At 5-year follow-up	Not possible to define as adequacy of surveillance not reported	In this retrospective cohort study, a number of plausible covariates were included in the multivariable analyses, reducing to some extent the risk of selection bias. Adjustment was carried out for OAC diagnosis, age, ethnicity, propensity to go into the surveillance group, comorbidities, total number of VA/GI visits, stage and treatment. The reasons for the comparator group not having surveillance was not explained.
MacDonald, 2000[13]	Surveillance endoscopies: defined as examinations done	Surveillance group: People with proven Barrett's oesophagus	Mortality from OAC All-cause mortality	Not possible to define as	This retrospective cohort study was at risk of critical bias.

Study	Intervention and comparison	Population	Outcomes	Sub-group (adequate surveillance or non-adequate surveillance)	Comments
	only for surveillance. Endoscopies to investigate deteriorating symptoms in a patient in the surveillance programme were not included as surveillance endoscopies. Vs No surveillance - this was in a group with Barrett's for whom surveillance was not regarded as appropriate. The main reasons were age >70 and co-existing serious illness.	who were potentially suitable for major surgery should a lesion be detected, which usually meant patients younger than 70 who had no serious coexisting disease (N=143) No surveillance group: were older (69 vs 57 years), less likely to be men (47% vs 60%), had a shorter length of metaplasia (73mm vs 81mm) and were less likely to have a stricture (5% vs 16%) compared to those in the surveillance group (N=266) Mean age (range): Surveillance group= 57 (17-69) years No surveillance group= 69 (17-94) years UK		adequacy of surveillance not reported	Firstly, the comparator group were systematically different to the surveillance group in prognostic characteristics. Secondly no statistical adjustments or matching were carried out.
Roberts, 2010[17]	Scheduled annual endoscopy with 4 quadrant biopsies every 2cm Vs	Patients with Barrett's metaplasia, and eventual OAC or HGD; fit for curative treatment (N=82)Mean age: not reported; age range: 46 to 93 years UK	All-cause mortality At 5-year follow-up	Adequate: Four quadrant biopsies every 2cm	This retrospective cohort study was at risk of critical bias. Firstly, the comparator group were systematically different to the surveillance group in prognostic characteristics. Secondly no statistical

Study	Intervention and comparison	Population	Outcomes	Sub-group (adequate surveillance or non-adequate surveillance)	Comments
	Single endoscopy with no scheduled programme of surveillance				adjustments or matching were carried out.
Royston, 2016[18]	Serial endoscopy and biopsy at 2-3-year intervals. Vs Clinical follow-up or lost to follow up	People with gastro-oesophageal reflux disease and Barrett's Oesophagus who later developed OAC (N=54) UK	Mortality from OAC At minimum 2-year follow-up	Not possible to define as adequacy of surveillance not reported	This retrospective cohort study was at risk of critical bias. Firstly, the comparator group were systematically different to the surveillance group in prognostic characteristics. Secondly no statistical adjustments or matching were carried out.
Theron, 2016[20]	Endoscopic surveillance: people underwent endoscopic surveillance if suitable every 2 years until they reached 75 years of age or developed co-morbidity that, in the opinion of the responsible clinician, precluded further surveillance due to the risks of oesophagectomy. Vs No surveillance: Patients failing to attend surveillance endoscopy despite being clinically indicated for surveillance.	All patients diagnosed with Barrett's between 1982 and 2007 at City Hospital, Birmingham, and between 1997 and 2007 at the adjacent Sandwell General Hospital, West Bromwich (N=431) Median age (range): endoscopic surveillance= 55.5 (51.2 to 66.6); no surveillance= 58 (49.2 to 63.6) UK	Mortality from OAC All-cause mortality Progression to OAC At 5-year follow-up	Adequate: Quadrantic biopsies were taken every 2 cm throughout the Barrett's segment in addition to targeted biopsies of any focal lesions and reported by a gastrointestinal histopathologist	This retrospective cohort study was also at risk of critical bias. Although the comparator group were clinically indicated for surveillance and did not receive it for non-clinical reasons, no attempt was made to adjust for any residual selection bias.
Verbeeck, 2014[21]	Endoscopic surveillance: Participation in an endoscopic surveillance program was defined as a prior Barrett's diagnosis 1 year or longer before OAC	All patients diagnosed with OAC between 1999 and 2009 in the Netherlands were selected from the nationwide Netherlands Cancer Registry (N=671)	Mortality from OAC Progression to type IV tumour stage	Not possible to define as adequacy of surveillance not reported	This study looked at other groups which have not been included in this review as they are less relevant to the aims of the review: inadequate

Study	Intervention and comparison	Population	Outcomes	Sub-group (adequate surveillance or non-adequate surveillance)	Comments
	diagnosis with at least one additional endoscopy with biopsies between the first histologic Barrett's and OAC diagnosis. Vs No surveillance: people with Barrett's not given any surveillance.	Age details not specified. Holland	At 2-year follow-up		surveillance and Barrett's unknown. In this retrospective cohort study, a number of plausible covariates were included in the multivariable analysis, reducing to some extent the risk of selection bias in the mortality analysis. Adjustments were made for age, gender, time between Barretts diagnosis and OAC diagnosis, dysplasia grade, hospital type, tumour grade, tumour stage, resectability of tumour and treatment. However, the progression to type IV tumour stage analysis is unadjusted and therefore prone to high levels of selection bias, particularly since the reasons for the comparator group not having surveillance was not explained.

1 See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: surveillance versus no surveillance

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no surveillance	Absolute risk difference (surveillance minus no surveillance) (95% CI)
Mortality from OAC at 2-5 years (**adjusted** hazard ratios)	1095 (2 studies) 2-5 years	LOW[1,3]	HR 0.77 (0.63, 0.93)	-	-
Mortality from OAC at 3 years (**adjusted** odds ratios)	139 (1 study) 2-10 years	VERY LOW[1,3]	OR 0.99 (0.36, 2.72)	-	-
Mortality from OAC at 2-10 years (risk ratios)	894 (3 studies) 2-10 years	VERY LOW[1,2,3]	Random effects RR 0.91 (0.37, 2.26)	49 per 1000	4 fewer per 1000 (from 31 fewer to 62 more)
All-cause mortality at 5 years (**adjusted** hazard ratios)	424 (1 study) 5 years	LOW[1,3]	HR 0.73 (0.52, 1.02)	-	-
All-cause mortality at 5-10 years (risk ratios)	922 (3 studies) 5-10 years	VERY LOW[1,2,3]	Random effects RR: 0.78 (0.39, 1.56)	391 per 1000	86 fewer per 1000 (from 239 fewer to 219 more)
Progression to OAC at 5 years	431 (1 study) 5 years	VERY LOW[1,3]	RR: 1.74 (0.82, 3.71)	49 per 1000	36 more per 1000 (from 9 fewer to 133 more)
Progression to type IV tumour stage	671 (1 study) 2 years	LOW[1]	RR: 0.33 (0.23, 0.47)	283 per 1000	190 fewer per 1000 (from 150 fewer to 218 fewer)

[1] Downgraded by one increment if moderate risk of bias and downgraded by two increments if serious or critical risk of bias
[2] Downgraded by two increments because of very serious heterogeneity (I^2 > 75%)
[3] Downgraded by one increment if the 95% CIs crossed one of the default MIDs (0.8 or 1.25) and downgraded by two increments if the 95% CIs crossed both of the default MIDs (0.8 and 1.25).

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

Four health economic evaluations with the relevant comparison were included in this review.[7, 8, 12, 15] These are summarised in the health economic evidence profile below (Table 4) and the health economic evidence tables in Appendix H. A fifth study was identified[19], which was a duplicate of one of the four included studies. This was attached to the study it duplicated under the study name in the evidence profile and evidence table.

1.1.7.2 Excluded studies

Three economic studies relating to this review question were identified but were excluded due to the availability of more applicable evidence.[5, 17, 22] These are listed in Appendix I, with reasons for exclusion given.

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

1.1.8 Summary of included economic evidence

Table 4: Health economic evidence profile: endoscopic surveillance versus no surveillance

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Garside 20067 Somerville 200819 (UK)	Partially applicable (a)	Potentially serious limitations (b)	Probabilistic Markov model based on systematic review of case series Population: Patients with BO Comparators: No surveillance Endoscopic surveillance and biopsy at 3-yearly intervals for ND BO, yearly intervals for LGD, and 3-monthly for HGD. Time horizon: 20 years	£918 (c)	-0.048 QALYs	Intervention 2 dominated	Probability Intervention 2 cost effective (£30K threshold): 11% Probability Intervention 2 dominated: 75% The model results were most sensitive to the recurrence rate of adenocarcinoma after oesophagectomy, the rate at which adenocarcinoma becomes symptomatic and the various health state utility scores, which all resulted in a cost per QALY below £30,000 per QALY gained.
Gordon 20148 (Australia)	Partially applicable (d)	Potentially serious limitations (e)	10-state probabilistic Markov model based on observational studies. Population: Patients with non-dysplastic BO. Comparators: No surveillance	(2−1): £4,408 (f) (3−1): £2,739 (f)	(2−1): 0.16 QALYs (3−1): 0.15 QALYs	(2−1): £28,436 per QALY gained (3−1): £17,899 per QALY	Probability Intervention 2 cost effective versus no surveillance (£46.7K threshold): 16% Probability Intervention 3 cost effective versus no surveillance (£46.7K threshold): 61% Results from one-way sensitivity analyses showed that annual progression rates from ND BO to HGD and from LGD to HGD were most sensitive to changes in the cost per QALY. A

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td></td><td></td><td></td><td>2-yearly endoscopic surveillance of patients with ND BO and 6-monthly surveillance of patients with LGD
Biomarker-modified endoscopic surveillance strategy (hypothetical)
Time horizon: 30 years</td><td></td><td></td><td></td><td>strategy of less frequent surveillance endoscopies also improved cost effectiveness (see table below).

<table><tr><td>Surveillance frequency</td><td>ICER</td></tr><tr><td>ND BO 3 yrs/ LGD 6 months</td><td>£22,516</td></tr><tr><td>ND BO 5 yrs/ LGD 6 months</td><td>£17,831</td></tr><tr><td>ND BO 3 yrs/ LGD annual</td><td>£14,838</td></tr><tr><td>ND BO none/ LGD annual</td><td>£4,718</td></tr></table></td></tr>
<tr><td>Lindblad 201712 (Australia)</td><td>Partially applicable (g)</td><td>Potentially serious limitations (h)</td><td>Adapted Markov model from Gordon 2014.
Population: Patients with a CLO who were enrolled in a BO surveillance programme.
Comparators:
No surveillance
Endoscopic surveillance in line with the Seattle protocol (2-yearly endoscopy in patients with known CLO, increased to 6-monthly in those with LGD.
Time horizon: 30 years</td><td>£7,126 (i)</td><td>0.451 QALYs</td><td>£15,797 per QALY gained</td><td>Probability Intervention 2 cost effective (£23.4K threshold): 63%

Scenario analysis explored the effect of excluding further patients from surveillance based on the length of the CLO segment. The costs per QALY when limiting surveillance to patients with a CLE length of less than 3cm was £16,721, and £51,671 when it was limited to patients with a CLO length of less than 4cm.

<table><tr><td></td><td>Probability Intervention 2 cost effective</td></tr></table></td></tr>
</table>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
							<table><tr><td></td><td>£20k</td><td>£30k</td></tr><tr><td>BO <2cm</td><td>58%</td><td>67%</td></tr><tr><td>BO <3cm</td><td>48%</td><td>55%</td></tr><tr><td>BO <4cm</td><td>40%</td><td>45%</td></tr></table>
Omidvari 202015 (The Netherlands)	Partially applicable (j)	Potentially serious limitations (k)	Microsimulation model Population: Patients with BO. Comparators: No surveillance Surveillance according to Dutch guidelines (ND short-segment BO: 5 years, ND long-segment BO: 3 years, LGD: 6-monthly & 1 year. Time horizon: lifetime.	£4,381 (l)	0.333 QALYs	£13,156 per QALY gained	The results were robust to changes to the age of the cohort, the progression rate of Barrett's oesophagus and participation rates for surveillance.

Abbreviations: BO= Barrett's oesophagus; CLO= columnar-lined oesophagus; EET= endoscopic eradication therapy; HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; LGD= low-grade dysplasia; ND= no dysplasia; OA= oesophageal adenocarcinoma; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) QALYs were not captured using the EQ-5D measure. Discounting for costs and outcomes were not in line with the current NICE reference case.

(b) The health outcomes were derived from case series. The model includes complications associated with oesophagectomy, but not those associated with endoscopy. Costs are from dated sources and may no longer reflect costs associated with current care in the NHS.

(c) Cost components incorporated: Pharmacological management, endoscopy (including biopsy), presurgical tests, surgical treatment of OA, treatment of complications from surgical treatment of OA, cost of untreatable OA.

(d) The Australian perspective is not in line with the NICE reference case. EQ-5D was valued using the Australian tariff. Costs and outcomes were not discounted in line with the NICE reference case.

(e) Progression rates of BO were taken from observational studies. Model results were based on a 90% attendance rate for surveillance appointments, which was not tested during sensitivity analysis.

(f) 2011 Australian dollar converted to UK pound. [16]. Cost components incorporated: biopsies, ultrasounds, imaging, endoscopic treatments and investigations, hospitalisations, in-hospital AEs, chemotherapy, radiotherapy, monitoring, stents and palliative care.

(g) Australian perspective is not in line with the NICE reference case. Costs and outcomes were not discounted in line with the NICE reference case.

(h) The sources for costs and utilities were not clearly defined.

(i) *2011 Australian dollar converted to UK pound. [16]}. Cost components incorporated: NR (but since the model was adapted from Gordon 2014, it is assumed to be what was reported there); biopsies, ultrasounds, imaging, endoscopic treatments and investigations, hospitalisations, in-hospital AEs, chemotherapy, radiotherapy, monitoring, stents and palliative care.*

(j) A UK perspective was not used in the analysis, and the study is therefore not in line with the NICE reference case. QALYs were not captured using the EQ-5D measure. Costs and outcomes were not discounted in line with the NICE reference case.

(k) Longer term outcomes of EET were extrapolated in the absence of evidence. It was assumed that all patients attended all surveillance and treatment sessions and that surveillance stopped at 80 years.2017 Euro converted to UK pound. 16. Cost components incorporated: Cost of endoscopy, initial EET treatment plus follow up costs and those resulting from complications, annual outpatient visits after oesophagectomy and care for stages 1-4 OA.

1.1.9 Economic model

This area was given a medium priority for new cost-effectiveness analysis.

1.1.10 Unit costs

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

Resource	Unit costs	Source
diagnostic endoscopic upper gastrointestinal tract procedure with biopsy, (FE21Z)	£554	National Schedule of NHS Costs. 2019/20

1.1.11 Evidence statements

Economic

- One cost utility analysis reported that no surveillance dominated endoscopic surveillance. This study was graded as partially applicable with potentially serious limitations.
- One cost-utility analysis reported that 2-yearly endoscopic surveillance of patients with ND BO and 6-monthly surveillance of patients with LGD was not cost effective compared to no surveillance (ICER: £28,436). This study was graded as partially applicable with potentially serious limitations.
- One cost-utility analysis reported that 2-yearly endoscopic surveillance of patients with ND BO and 6-monthly surveillance of patients with LGD was cost effective compared to no surveillance in patients with columnar-lined oesophagus (ICER: £15,797). This study was graded as partially applicable with potentially serious limitations.
- One cost-utility analysis reported that endoscopic surveillance according to Dutch national guidelines was cost effective compared to no surveillance (ICER: £13,156). This study was graded as partially applicable with potentially serious limitations.

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, health related quality of life, progression of dysplasia, progression to cancer or progression of stage of cancer, and adverse events (such as those related to sedation, bleeding, pain and perforation). For purposes of decision-making all outcomes were equally regarded as being of critical importance. No evidence was identified for the outcomes of health-related quality of life, progression to dysplasia, or adverse events.

1.1.12.2 The quality of the evidence

The quality of the evidence was rated as low or very low. One reason for this was serious or critical risk of bias for the majority of the outcomes. Serious or critical risk of bias resulted from selection bias in studies due to their observational design. Although three studies used some form of statistical adjustment to reduce potential bias, this is unlikely to have reduced selection bias to the levels expected in randomised studies. In the other four studies, there were no attempts to reduce confounding factors, leading to critical risk of bias. Another important factor explaining the low or very low grading of evidence was the serious or very serious imprecision in the majority of the effect estimates. None of the studies directly referred to 'white light endoscopy' and used the more general term 'endoscopy' instead. However, the committee agreed that this should not lead to downgrading the evidence for

indirectness because high resolution white light endoscopy is the standard endoscopy procedure that is widely used in clinical practice and therefore the term 'endoscopy' tends to indicate 'white light endoscopy' by default. The committee was confident that any endoscopy that was not high resolution white light endoscopy would have been specified.

The committee agreed that the data from the adjusted studies should be given more weight than the unadjusted studies. This was based on the observation that the unadjusted studies carried high risk of selection bias, which made it almost impossible to make valid inferences about efficacy. Discussion therefore focussed on the evidence from the three adjusted studies.[2,4, 21]

1.1.12.3 Benefits and harms

The evidence from two adjusted observational studies showed that endoscopic surveillance using high resolution white light reduced disease-specific and all-cause mortality, reducing the instantaneous risk by almost 30% compared to no surveillance. However, one study showed a contradictory result, demonstrating no difference in the odds of mortality between surveillance and no surveillance. One explanation for this contradiction was an uncertainty about the quality of surveillance performed in the latter study (where surveillance was any esophagogastroduodenoscopy performed principally for cancer surveillance of a previously documented Barrett's oesophagus, the adequacy of which was not reported), which met with agreement within the committee. In addition, the quality of the evidence in the adjusted studies was given a higher quality rating than that of the unadjusted study because of a more thorough statistical adjustment process. Therefore, the committee concluded that the evidence from the adjusted studies was the most valid and should be used to inform recommendations. On this basis, because the evidence from the adjusted studies supported surveillance in terms of disease-specific and all-cause mortality , the committee agreed that surveillance should be used in people who are suitable for endoscopy.

The committee discussed how the evidence did not include any data on adverse events of surveillance using high resolution white light, preventing a full evaluation of benefits and harms. It was noted that the complications of endoscopy were well-established, including bleeding, perforation, and infection. The committee agreed that these would be considered on a patient-by-patient basis because the frequency and consequences of such complications are not homogeneous and will vary depending on a complex array of factors including age and co-morbidities. It was agreed that a discussion about possible adverse effects should be included in consultation with the patient and agreed by consensus that a recommendation should be made to discuss both the benefits and risks of endoscopic surveillance with a person who has been newly diagnosed with Barrett's oesophagus. The committee also noted the absence of evidence on quality of life and progression of dysplasia but thought that the existing evidence that had been considered was sufficient to formulate a recommendation to offer white light endoscopy for surveillance (also see evidence review 2.1b Diagnostic accuracy of endoscopic surveillance).

1.1.12.4 Cost effectiveness and resource use

Four economic studies were included in the review. All were in a Barrett's oesophagus population.

One study took a UK perspective with a time horizon of 20 years. Health outcomes were based on a systematic review of case series. QALYs were captured using the EQ-5D. Costs were based on UK NHS expenditure but were taken from dated sources. Furthermore, the discount rates applied to costs and health outcomes were not in line with the current NICE reference case. This study was graded as being partially applicable with potentially serious limitations.

Two studies took an Australian perspective and calculated QALYs using the EQ-5D measure. Both studies applied the same Markov model with the only difference between the

two being the initial population; the first study was based on a population where 95% had a diagnosis of non-dysplastic Barrett's, 4% had a diagnosis of low-grade dysplasia and 1% had a diagnosis of high-grade dysplasia, while the second study stratified the population to only include patients with columnar-lined oesophagus who attended follow-up surveillance sessions after the initial index endoscopy and did not progress to high-grade dysplasia or oesophageal adenocarcinoma in the first year. Progression rates for Barrett's oesophagus in the model were taken from observational studies and QALYs were captured using the EQ-5D. Costs and resource use were based on national price schedules for public hospitals. The discounting rates applied to costs and health outcomes were not in line with the current NICE reference case. Both studies were graded overall as being partially applicable with potentially serious limitations.

The final study took the perspective of The Netherlands. A microsimulation model based on an observational study with a lifetime horizon was used. Utilities were taken from literature or expert feedback. Costs were based on average public hospital prices and resource used was based on a retrospective chart review. The discounting rates applied to costs and health outcomes were not in line with the current NICE reference case. This study was graded as being partially applicable with potentially serious limitations.

There was variation amongst the results of the cost effectiveness of endoscopic surveillance versus no surveillance with one study reporting it was dominated by no surveillance, one study reporting the cost per QALY being greater than £20,000 and the other two studies reporting it was cost effective at a cost per QALY threshold of £20,000.

The committee discussed the reasons for this observed variation. It was noted that the dominance of endoscopic surveillance by no surveillance in one study was driven by an abnormally high utility score being applied to the asymptomatic adenocarcinoma health state which favoured the no surveillance arm since QALY gains were accrued during a period where costs of treatment were being deferred until patients progressed from asymptomatic to symptomatic adenocarcinoma. The committee agreed that this was an implausible scenario. They also noted that the study was dated and based on costs that are unlikely to be reflective of current NHS care. Given these limitations, the committee decided to put little weight on this study for decision-making purposes.

Of the three remaining studies, the committee noted that the incremental costs as well as the incremental QALYs were highest in the study that stratified the Barrett's population, suggesting that a targeted approach to surveillance is cost effective at a threshold of £20,000 per QALY gained.

Of the two studies remaining looking at the general Barrett's population, one study that based surveillance on the Seattle protocol suggested that it was not cost effective at a cost per QALY threshold while the other study that was based on Dutch guidelines suggested that it was. The committee noted that incremental costs in both studies were similar, and the main driver of cost effectiveness was incremental QALY gains associated with endoscopic surveillance. They also noted that the first study ran sensitivity analyses adjusting the frequency of surveillance and that the cost per QALY fell below the £20,000 threshold when the frequency was adjusted to 3-yearly surveillance in non-dysplastic Barrett's oesophagus and yearly surveillance in low-grade dysplasia). Current UK guidelines for surveillance are flexible and allow for surveillance intervals of between 3-5 years in non-dysplastic Barrett's oesophagus and 6 months in low-grade dysplasia. However, given that patients with low-grade dysplasia only account for 3-4% of the total Barrett's population, the higher frequency of surveillance in the UK guidelines versus the sensitivity analysis is unlikely to substantially change the overall cost per QALY. It was also noted that the frequency of endoscopic surveillance according to the UK guidelines were similar to the Dutch guidelines which was also reported to be cost effective; in the Dutch guidelines, patients with short-segment non-dysplastic Barrett's oesophagus are surveyed every 5 years, patients with long-segment non-

dysplastic surveillance are surveyed every 3 years and patients with low-grade dysplasia are seen 6-monthly and then annually.

Given this, the committee agreed that it was appropriate to continue to recommend endoscopic surveillance for patients with Barrett's oesophagus. See also Evidence Review 2.3 on frequency of surveillance.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1 – 1.3.4.

1.1.14 References

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Appendices

Appendix A – Review protocols

A1 Review protocol for white-light endoscopy

ID	Field	Content
0.	PROSPERO registration number	CRD42021267452
1.	Review title	The clinical and cost effectiveness of endoscopic surveillance (white light endoscopy)
2.	Review question	For adults with Barrett's oesophagus, what is the clinical and cost effectiveness of endoscopic surveillance using white light endoscopy?
3.	Objective	To assess the efficacy and cost effectiveness of endoscopic surveillance of people 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 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) Exclusion: Those with disease that does not fit within definition of Barrett's
7.	Intervention	• white light endoscopy

8.	Comparator	• No Surveillance (disease extent doesn't meet definition; benefit of surveillance isn't appropriate)
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 • Systematic Reviews 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	Different endoscopic surveillance techniques are used for ongoing surveillance in people with Barrett's Oesophagus. This review aims to assess the clinical and cost effectiveness the gold standard / reference surveillance test compared to no surveillance.
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 • Health related quality of life (validated scores) • Progression of dysplasia • Progression to cancer and stage • Adverse events (such as sedation related, bleeding, pain, perforation)

		Time points: beyond 1 year of follow up (minimum) up to longest follow up period
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

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 OACh 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 OACh 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 OACh 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 sufficient data is available, WinBUGS will be used for network meta-analysis, if possible, given the data identified.
17.	Analysis of sub-groups	Stratification: Subgrouping:

		If serious or very serious heterogeneity (I2>50%) is present, sub-grouping will occur according to the following strategies: Adequate surveillance (based on the number of biopsies) 4 biopsies every 2 cm of barrett's vs Non-adequate surveillance Duration of procedure		
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: Amy Crisp Gill Ritchie Lina Gulhane Muksitar Rahman		

		Stephen Deed Vimal Bedia
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 OACh guideline committee meeting. Before OACh 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: [NICE guideline webpage].
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	

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2

3

1 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). [14] **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.

1

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. [14]

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. Search filters were applied to the search where appropriate.

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 April 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 April 2022	Randomised controlled trials Systematic review studies 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	
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 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.	*Endoscopy, Gastrointestinal/
38.	Capsule Endoscopy/
39.	Esophagoscopy/
40.	Gastroscopy/
41.	(videoendoscop* or endomicroscop* or spectroscop* or endocytoscop* or oesophagoscop* or esophagoscop* or gastroscop*).ti,ab.
42.	(endoscop* adj3 (imag* or diagn* or identif* or surveillanc* or monitor* or observ* or detect*)).ti,ab.
43.	((capsule or transnasal or nasal) adj2 endoscop*).ti,ab.

44.	exp Optical Imaging/
45.	exp Acetic Acid/
46.	Molecular Imaging/
47.	(molecular adj3 (imag* or endoscop*)).ti,ab.
48.	((magnif* or high resolution or high definition) adj3 endoscop*).ti,ab.
49.	(chromatograph* or chromoendoscop* or chromoscop* or volumetric laser* or acetic acid or methylene blue or indigo carmine or narrow band or white light or blue laser or blue light or flexible spectral imaging colo?r enhancement or autofluorescen* or fluorescen* or optical coherence tomography or trimodal or tri modal or optical enhancement).ti,ab.
50.	exp Artificial Intelligence/
51.	(artificial intelligence or (computer adj (assisted or aided)) or ((deep or machine) adj learning) or neural network*).ti,ab.
52.	(wide area transepithelial sampling or WATS3D or WATS 3D).ti,ab.
53.	((endoscop* or oesophagoscop* or esophagoscop*) adj2 brush*).ti,ab.
54.	(HRE or WLE or NBI or BLI or FICE or AFI or OCT or ETMI or OE or AI or CAD).ti,ab.
55.	or/37-54
56.	36 and 55
57.	randomized controlled trial.pt.
58.	controlled clinical trial.pt.
59.	randomi#ed.ab.
60.	placebo.ab.
61.	randomly.ab.
62.	clinical trials as topic.sh.
63.	trial.ti.
64.	or/57-63
65.	Meta-Analysis/
66.	Meta-Analysis as Topic/
67.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
68.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
69.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71.	(search* adj4 literature).ab.
72.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
73.	cochrane.jw.
74.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
75.	or/65-74
76.	56 and (64 or 75)

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.	*gastrointestinal endoscopy/
37.	gastroscopy/
38.	*endoscopy/
39.	endocytoscopy/
40.	high resolution endoscopy/
41.	magnifying endoscopy/
42.	narrow band imaging/
43.	videoendoscopy/
44.	white light endoscopy/
45.	capsule endoscopy/
46.	esophagoscopy/
47.	exp fluorescence imaging/
48.	exp acetic acid/
49.	molecular imaging/

50.	chromoendoscopy/
51.	exp artificial intelligence/
52.	(videoendoscop* or endomicroscop* or spectroscop* or endocytoscop* or oesophagoscop* or esophagoscop* or gastroscop* or chromatograph* or chromoendoscop* or chromoscop* or volumetric laser or acetic acid or methylene blue or indigo carmine or narrow band or white light or blue laser or blue light or flexible spectral imaging colo?r enhancement or autofluorescen* or fluorescen* or optical coherence tomography or trimodal or tri modal or optical enhancement).ti,ab.
53.	(endoscop* adj3 (imag* or diagn* or identif* or surveillanc* or monitor* or observ* or detect*)).ti,ab.
54.	((capsule or transnasal or nasal) adj2 endoscop*).ti,ab.
55.	(molecular adj3 (imag* or endoscop*)).ti,ab.
56.	((magnif* or high resolution or high definition) adj3 endoscop*).ti,ab.
57.	(artificial intelligence or (computer adj (assisted or aided)) or ((deep or machine) adj learning) or neural network*).ti,ab.
58.	(wide area transepithelial sampling or WATS3D or WATS 3D).ti,ab.
59.	((endoscop* or oesophagoscop* or esophagoscop*) adj2 brush*).ti,ab.
60.	(HRE or WLE or NBI or BLI or FICE or AFI or OCT or ETMI or OE or AI or CAD).ti,ab.
61.	or/36-60
62.	35 and 61
63.	random*.ti,ab.
64.	factorial*.ti,ab.
65.	(crossover* or cross over*).ti,ab.
66.	((doubl* or singl*) adj blind*).ti,ab.
67.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
68.	crossover procedure/
69.	single blind procedure/
70.	randomized controlled trial/
71.	double blind procedure/
72.	or/63-71
73.	Systematic Review/
74.	Meta-Analysis/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	62 and (72 or 83)

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: [Endoscopy, Gastrointestinal] this term only
#18.	MeSH descriptor: [Capsule Endoscopy] this term only
#19.	MeSH descriptor: [Esophagoscopy] this term only
#20.	MeSH descriptor: [Gastroscopy] this term only
#21.	(videoendoscop* or endomicroscop* or spectroscop* or endocytoscop* or oesophagoscop* or esophagoscop* or gastroscop*):ti,ab
#22.	(endoscop* near/3 (imag* or diagn* or identif* or surveillanc* or monitor* or observ* or detect*)):ti,ab
#23.	((capsule or transnasal or nasal) near/2 endoscop*):ti,ab
#24.	MeSH descriptor: [Optical Imaging] explode all trees
#25.	MeSH descriptor: [Acetic Acid] explode all trees
#26.	MeSH descriptor: [Molecular Imaging] this term only
#27.	(molecular near/3 (imag* or endoscop*)):ti,ab
#28.	((magnif* or high resolution or high definition) near/3 endoscop*):ti,ab
#29.	(chromatograph* or chromoendoscop* or chromoscop* or volumetric laser or acetic acid or methylene blue or indigo carmine or narrow band or white light or blue laser or blue light or flexible spectral imaging colo?r enhancement or autofluorescen* or fluorescen* or optical coherence tomography or trimodal or tri modal or optical enhancement):ti,ab
#30.	MeSH descriptor: [Artificial Intelligence] explode all trees
#31.	(artificial intelligence or (computer next (assisted or aided)) or ((deep or machine) next learning) or neural network*):ti,ab
#32.	(wide area transepithelial sampling or WATS3D or WATS 3D):ti,ab
#33.	((endoscop* or oesophagoscop* or esophagoscop*) near/2 brush*):ti,ab
#34.	(HRE or WLE or NBI or BLI or FICE or AFI or OCT or ETMI or OE or AI or CAD):ti,ab
#35.	(or #17-#34)
#36.	#16 and #35

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:("endoscop* imag*" OR "endoscop* diagn*" OR "endoscop* identif*" OR "endoscop* surveillanc*" OR "endoscop* monitor*" OR "endoscop* observ*" OR "endoscop* detect*" OR "capsule endoscop*" OR "transnasal endoscop*" OR "nasal endoscop*" OR "magnif* endoscop*" OR "high resolution endoscop*" OR "high definition endoscop*" OR videoendoscop* OR endomicroscop* OR spectroscop* OR endocytoscop* OR oesophagoscop* OR esophagoscop* OR gastroscop* OR chromatograph* OR chromoendoscop* OR chromoscop* OR "volumetric laser" OR "acetic acid" OR "methylene blue" OR "indigo carmine" OR "narrow band" OR "white light" OR "blue laser" OR "blue light" OR "flexible spectral imaging" OR autofluorescen* OR fluorescen* OR "optical coherence tomography" OR trimodal OR "tri modal" OR "optical enhancement" OR "artificial intelligence" OR "computer assisted" "computer aided" OR "deep learning" OR "machine learning" OR "neural network" OR "wide area transepithelial sampling" OR WATS3D OR "WATS 3D") OR abstract:("endoscop* imag*" OR "endoscop* diagn*" OR "endoscop* identif*" OR "endoscop* surveillanc*" OR "endoscop* monitor*" OR "endoscop* observ*" OR "endoscop* detect*" OR "capsule endoscop*" OR "transnasal endoscop*" OR "nasal endoscop*" OR "magnif* endoscop*" OR "high resolution endoscop*" OR "high definition endoscop*" OR videoendoscop* OR endomicroscop* OR spectroscop* OR endocytoscop* OR oesophagoscop* OR esophagoscop* OR gastroscop* OR chromatograph* OR chromoendoscop* OR chromoscop* OR "volumetric laser" OR "acetic acid" OR "methylene blue" OR "indigo carmine" OR "narrow band" OR "white light" OR "blue laser" OR "blue light" OR "flexible spectral imaging" OR autofluorescen* OR fluorescen* OR "optical coherence tomography" OR trimodal OR "tri modal" OR "optical enhancement" OR "artificial intelligence" OR "computer assisted" "computer aided" OR "deep learning" OR "machine learning" OR "neural network" OR "wide area transepithelial sampling" OR WATS3D OR "WATS 3D")

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
	Quality of Life 1946 – 29 April 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language

Database	Dates searched	Search filters and limits applied
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

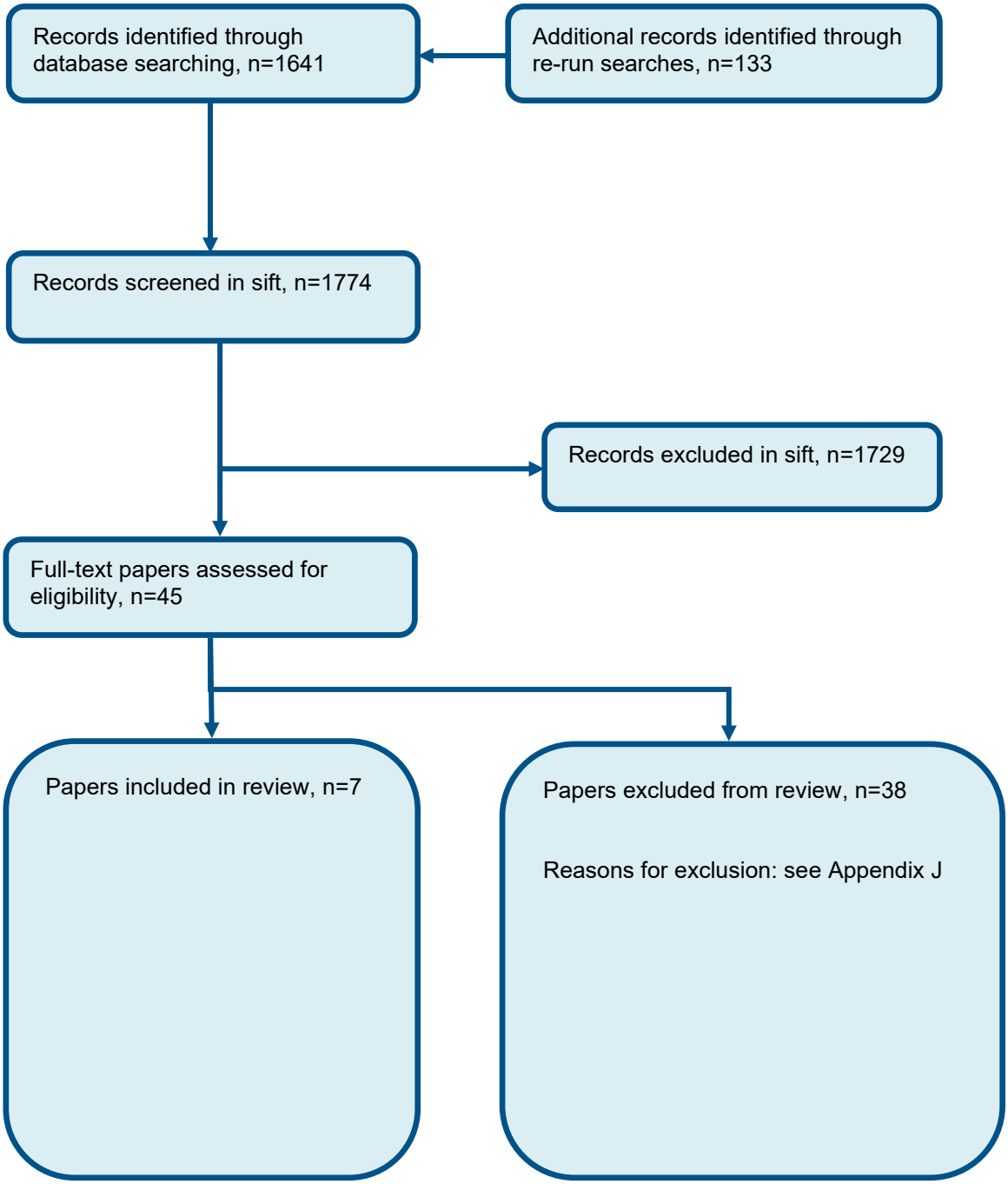
#1.	MeSH DESCRIPTOR Barrett Esophagus EXPLODE ALL TREES
#2.	(barrett*)
#3.	(speciali*) AND (epithel* or oesophag* or esophag* or mucos*)
#4.	(column*) AND (epithel* or oesophag* or esophag* or mucos* or lined or lining or metaplas*)
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Precancerous Conditions 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 surveillance versus no surveillance



Appendix D – Effectiveness evidence

Corley, 2013

Bibliographic Reference	Corley, D. A.; Mehtani, K.; Quesenberry, C.; Zhao, W.; de Boer, J.; Weiss, N. S.; Impact of endoscopic surveillance on mortality from Barrett's esophagus-associated esophageal adenocarcinomas; Gastroenterology; 2013; vol. 145 (no. 2); 312-9.e1

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study location	USA
Study setting	Community-based setting

Study dates	1995-2009
Sources of funding	Supported by US National Institutes of Health grant RO1 DK63616; the Kaiser Permanente Research Project on Genes, Environment and Health; and a Kaiser Permanente Community Benefits Grant
Inclusion criteria	Cases were adults who were diagnosed with oesophageal or gastroesophageal junction adenocarcinoma before September 2007; had a Barrett's oesophagus diagnosis 6 months or more before their cancer diagnosis; and subsequently died of esophageal/gastroesophageal junction adenocarcinoma or its complications before December 31, 2009. Cancers were identified using the region's Surveillance, Epidemiology, and End Results cancer registry. Controls were KPNC members with a diagnosis of Barrett's oesophagus who did not die of oesophageal or gastroesophageal junction adenocarcinoma through the end of the follow-up evaluation. Controls were matched to cases by age at Barrett's esophagus diagnosis, year of Barrett's esophagus diagnosis, medical center of Barrett's oesophagus diagnosis, sex, and race.
Exclusion criteria	Patients were excluded if they had only gastric-type metaplasia of the esophagus, had columnar metaplasia without intestinal metaplasia, lacked endoscopic changes indicating Barrett's esophagus; or lacked an esophageal biopsy.
Recruitment / selection of participants	Review of the case notes of the cases and controls.
Intervention(s)	A surveillance endoscopy was any esophagogastroduodenoscopy performed principally for cancer surveillance of a previously documented Barrett's esophagus, not for symptoms. A patient in surveillance was someone who had at least 1 surveillance endoscopy within the 3 years before the index date. Included as surveillance examinations were those that diagnosed the index cancer if the examination was performed only for surveillance and not for symptoms. Assignment of surveillance status used endoscopy reports, pathology requests, and outpatient visits.
Comparator	No surveillance. No information was given in the article why some people did not have surveillance - whether it was due to it not being clinically indicated, or whether it was refused by the patient, or simply not available.
Number of participants	139
Duration of follow-up	3 years

Indirectness	White light endoscopy not specifically mentioned.
Additional comments	Association between surveillance and death was analysed using conditional logistic regression, adjusting for dysplasia status.

Study arms

Surveillance (N = 82)
A surveillance endoscopy was any esophagogastroduodenoscopy performed principally for cancer surveillance of a previously documented Barrett's esophagus, not for symptoms. A patient in surveillance was someone who had at least 1 surveillance endoscopy within the 3 years before the index date. Included as surveillance examinations were those that diagnosed the index cancer if the examination was performed only for surveillance and not for symptoms. A 3-year interval was selected a priori because it is the shortest recommended interval in guidelines for persons without dysplasia and, thus, the one most likely to be associated with a mortality benefit. Assignment of surveillance status used endoscopy reports, pathology requests, and outpatient visits. The N of 82 has been calculated from the fact that there were 55.3% of 38 cases [case=person who died of OAC secondary to BE] with surveillance and 60.4% of 101 controls [control=person with BE not dying of OAC] with surveillance; (0.553x38) + (0.604x101)=82

No surveillance (N = 57)
Did not receive surveillance, but were suffering from BE. This group did not exclude people with OAC, merely excluding those people dying from OAC. The N of 61 is calculated from the fact that there were 139 in the study and 82 with surveillance. Therefore there must have been 139-82=57 with no surveillance

Characteristics

Study-level characteristics

Characteristic	Study (N = 139)
% Female No of events	n = 12 ; % = 8.63

Arm-level characteristics

Characteristic	Surveillance (N = 82)	No surveillance (N = 57)
Mean age (SD) Mean (SD)	73.5 (8.2)	73.8 (8.1)
Ethnicity - Non Hispanic white No of events	n = 36 ; % = 94.7	n = 95 ; % = 94.1

Outcomes

Study timepoints

- 3 year

Surveillance v no surveillance

Outcome	Surveillance vs No surveillance, 3 year, N2 = 82, N1 = 57
Mortality Odds ratio/95% CI	0.99 (0.36 to 2.75)

Adjusted for dysplasia status, and the controls were also matched to the cases for several plausible factors. The unadjusted OR is 0.81: unadjusted odds of dying when on surveillance=21/61 and unadjusted odds of dying when on no surveillance= 17/40. Ratio of these odds is 0.81

El-Serag, 2016

Bibliographic Reference	El-Serag, H. B.; Naik, A. D.; Duan, Z.; Shakhatreh, M.; Helm, A.; Pathak, A.; Hinojosa-Lindsey, M.; Hou, J.; Nguyen, T.; Chen, J.; Kramer, J. R.; Surveillance endoscopy is associated with improved outcomes of oesophageal adenocarcinoma detected in patients with Barrett's oesophagus; Gut; 2016; vol. 65 (no. 8); 1252-60

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with	NA

this study included in review	
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	USA
Study setting	National Veterans Affairs Hospitals
Study dates	2004-2009
Sources of funding	This work was funded in part by US Department of Health and Human Services-National Institutes of Health-National Cancer Institute grant R01 NCI RC4 155844, the Centre for Innovations in Quality, Effectiveness and Safety (CIN#13-413), and the Texas Digestive Disease Centre NIH DK58338. HE-S is also supported by NIDDK K24-04-107.
Inclusion criteria	Patients who were >18 years of age at BE index date and had at least 1 year of follow-up after the index Barrett's endoscopy as well as before their last VA visit or date of oesophageal cancer.
Exclusion criteria	Patients with Barrett's with conditions diagnosed within 5 years prior to and up to the Barrett's index date, which may affect the likelihood of developing OAC (previous oesophageal cancer, gastroesophageal resection, bariatric surgery) or overall survival and thus the eligibility to receive endoscopic surveillance (any GI cancer, abdominal cancer, decompensated liver disease, metastatic cancer, cancer therapy).
Recruitment / selection of participants	The study sampling frame consisted of patients with BE who developed oesophageal cancer subsequent to BE diagnosis. The Barrett's cohort was defined by the presence of International Classification of Diseases (ICD)-9 code 530.85 combined with an endoscopy within 1 year before or after the date of the first BE code during fiscal year (FY) 2004–2009 (N=40 239).
Intervention(s)	Barrett's Surveillance included patients who received surveillance endoscopy for non-dysplastic Barrett's or surveillance endoscopy for Barrett's with dysplasia initially detected as a result of Barrett's surveillance.
Comparator	Patients whose OAC was initially detected on diagnostic endoscopy, screening endoscopy, unknown indication for endoscopy or surveillance endoscopy for dysplasia originally detected in non- Barrett's surveillance endoscopy

Number of participants	424
Duration of follow-up	5 years (mean)
Indirectness	Not described specifically as white light endoscopy.
Additional comments	Logistic regression. Adjustments were made for year of OAC diagnosis, age, race, propensity of EGD, comorbidity score, total number of VA visits and GI clinic visits, stage and treatment.

Study arms

BE endoscopic surveillance (N = 209)
BE endoscopic surveillance was one broad category that included patients who received surveillance endoscopy for non-dysplastic BE or surveillance endoscopy for BE with dysplasia initially detected as a result of BE surveillance.

Non BE surveillance diagnostic endoscopy (N = 215)
Non-surveillance was the second broad category and consisted of patients whose OAC was initially detected on diagnostic endoscopy, screening endoscopy, unknown indication for endoscopy or surveillance endoscopy for dysplasia originally detected in non-BE surveillance endoscopy. This latter group of patients, while they may gain benefits of surveillance, was not detected through routine BE surveillance, which is performed in nondysplastic BE.

Characteristics

Study-level characteristics

Characteristic	Study (N = 424)
% Female No of events	n = 1 ; % = 0.24

Arm-level characteristics

Characteristic	BE endoscopic surveillance (N = 209)	Non BE surveillance diagnostic endoscopy (N = 215)
Mean age Mean (SD)	60.6 (9.6)	63.3 (10)
Propensity score to receive any endoscopy after BE diagnosis - number in 4th quartile of 0.62 to 0.87 No of events	n = 98 ; % = 46.9	n = 75 ; % = 34.9
Comorbidity score of 2 or more No of events	n = 50 ; % = 23.9	n = 50 ; % = 23.3

Outcomes

Study timepoints

- 5 year

BE surveillance vs non BE surveillance

Outcome	BE endoscopic surveillance vs Non BE surveillance diagnostic endoscopy, 5 year, N2 = 209, N1 = 215
All cause mortality Hazard ratio/95% CI	0.73 (0.52 to 1.01)
OAC related mortality Hazard ratio/95% CI	0.72 (0.51 to 1.01)

Macdonald, 2000

Bibliographic Reference	Macdonald, C. E.; Wicks, A. C.; Playford, R. J.; Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study; BMJ; 2000; vol. 321 (no. 7271); 1252-5

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	UK
Study setting	Secondary care - general Hospital

Study dates	1984-1994
Sources of funding	No funding
Inclusion criteria	All patients with proved Barrett's oesophagus were considered for entry into the surveillance programme. To be eligible the patient had to be potentially suitable for major surgery should a lesion be detected, which usually meant patients younger than 70 who had no serious coexisting disease.
Exclusion criteria	None reported
Recruitment / selection of participants	Retrospective perusal of patient notes
Intervention(s)	Surveillance endoscopies were defined as examinations done only for surveillance. Endoscopies to investigate deteriorating symptoms in a patient in the surveillance programme were not included as surveillance endoscopies.Biopsy samples were usually taken from all four quadrants at the midpoint of the affected mucosa, with additional multiple samples taken from any region that showed additional abnormality. The affected area was not mapped. Barrett's mucosa was reported if glandular mucosa was present in a biopsy sample from the oesophagus. Any coexisting intestinal metaplasia (recognised by prominent goblet cells) was also reported. Areas of dysplasia were defined as mild, moderate, or severe depending on the degree of nuclear atypia and pseudostratification.
Comparator	No surveillance - this was in a group with Barrett’s for whom surveillance was not regarded as appropriate. The main reasons were age >70 and co-existing serious illness. The no surveillance group were older (69 vs 57 years), less likely to be men (47% vs 60%), had a shorter length of metaplasia (73mm vs 81mm) and were less likely to have a stricture (5% vs 16%) compared to those in the surveillance group.
Number of participants	409
Duration of follow-up	10 years
Indirectness	White light endoscopy not directly mentioned

Additional comments	Descriptive analysis without adjustment for potential confounding. This is a particularly serious flaw given that the groups were systematically different in terms of prognostic characteristics.

Study arms

Surveillance (N = 143)
Surveillance endoscopies were defined as examinations done only for surveillance of Barrett's. Endoscopies to investigate deteriorating symptoms in a patient in the surveillance programme were not included as surveillance endoscopies.

No surveillance (N = 266)
These were people deemed not suitable for surveillance. They were therefore very different in characteristics and prognostic factors.

Characteristics

Study-level characteristics

Characteristic	Study (N = 409)
% Female No of events	n = 254 ; % = 62.1

Arm-level characteristics

Characteristic	Surveillance (N = 143)	No surveillance (N = 266)
Mean age (SD) Range	17 to 69	17 to 94
Mean age (SD) Mean	57	69

Outcomes

Study timepoints

- 10 year

Surveillance v non surveillance

Outcome	Surveillance, 10 year, N = 143	No surveillance, 10 year, N = 266
Death due to OAC No of events	n = 3 ; % = 2.09	n = 1 ; % = 0.38
Any mortality No of events	n = 33 ; % = 23.07	n = 104 ; % = 39.09

Roberts, 2010

Bibliographic Reference	Roberts, K. J.; Harper, E.; Alderson, D.; Hallissey, M.; Long-term survival and cost analysis of an annual Barrett's surveillance programme; European Journal of Gastroenterology and Hepatology; 2010; vol. 22 (no. 4); 399-403

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	UK
Study setting	Secondary care
Study dates	1994-2001
Sources of funding	No funding was received

Inclusion criteria	Barrett's metaplasia, and eventual OAC or HGD; fit for curative treatment
Exclusion criteria	Patients unfit for curative surgery
Recruitment / selection of participants	Perusal of patient data
Intervention(s)	Scheduled annual endoscopy with 4 quadrant biopsies every 2cm
Comparator	Single endoscopy with no scheduled programme of surveillance
Number of participants	82
Duration of follow-up	5 years minimum
Indirectness	White light endoscopy not described; comparator utilised a single endoscopy
Additional comments	No adjustment for confounding made

Study arms

Surveillance (N = 8)
Patients with Barrett's undergoing scheduled annual endoscopy with 4 quadrant biopsies every 2cm, who developed either OAC or high grade dysplasia (HGD) during follow up.

Non-surveillance (N = 74)
This group had received a single endoscopy (thus downgraded for comparator indirectness because strictly speaking the comparator is 'no endoscopy') but this was not part of a systematic annual programme. This group all had OAC or HGD picked up on this single endoscopy, and were followed up for the same time period as the intervention group. They are described as the prevalence group in the article.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 82)**
% Female No of events	n = 28 ; % = 34.14
Mean age (SD) Range	46 to 93

Outcomes

Study timepoints
- 5 year

Surveillance versus no surveillance

Outcome	Surveillance, 5 year, N = 8	Non-surveillance, 5 year, N = 74
All cause mortality No of events	n = 4 ; % = 50	n = 72 ; % = 97.3

Royston, 2016

Bibliographic Reference	Royston, C.; Caygill, C.; Charlett, A.; Bardhan, K. D.; The evolution and outcome of surveillance of Barrett's oesophagus over four decades in a UK District General Hospital; European Journal of Gastroenterology and Hepatology; 2016; vol. 28 (no. 12); 1365-1373

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA

Study type	Retrospective cohort study
Study location	UK
Study setting	Secondary care - general hospital
Study dates	1977-2013
Sources of funding	None reported
Inclusion criteria	People with gastro-oesophageal reflux disease and Barrett's Oesophagus who later developed OAC.
Exclusion criteria	Not reported
Recruitment / selection of participants	Perusal of patient database
Intervention(s)	Serial endoscopy and biopsy at 2-3 year intervals.
Comparator	Clinical follow up or lost to follow up
Number of participants	54
Duration of follow-up	Minimum of 2 years
Indirectness	Endoscopy not described as white light endoscopy
Additional comments	No adjustment for confounding - simple comparisons of risks

Study arms

Surveillance (N = 37)
Endoscopic surveillance. serial endoscopy at 2-3 yearly intervals. Endoscopy findings recorded in detail supplemented by sketches and photographs. Documentation in line with Prague classification

No endoscopic surveillance/lost to follow up (N = 17)
Little description provided, except that this group were only given clinical surveillance or lost to follow up, and not given the endoscopic surveillance programme.

Outcomes

Study timepoints

- 2 year (This was the minimum follow up although most follow up periods were considerably longer)

Surveillance versus no surveillance

Outcome	Surveillance, 2 year, N = 37	No endoscopic surveillance/lost to follow up, 2 year, N = 17
Mortality from OAC No of events	n = 19 ; % = 51	n = 15 ; % = 88

Theron, 2016

Bibliographic Reference	Theron, B. T.; Padmanabhan, H.; Aladin, H.; Smith, P.; Campbell, E.; Nightingale, P.; Cooper, B. T.; Trudgill, N. J.; The risk of oesophageal adenocarcinoma in a prospectively recruited Barrett's oesophagus cohort; United european gastroenterology journal; 2016; vol. 4 (no. 6); 754-761

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	None
Study type	Retrospective cohort study
Study location	UK
Study setting	Secondary Care in large UK city - General Hospital
Study dates	1982-2007 at City Hospital Birmingham and 1997-2007 at Sandwell General Hospital

Sources of funding	No sources of finding
Inclusion criteria	All patients diagnosed with Barrett's between 1982 and 2007 at City Hospital, Birmingham, and between 1997 and 2007 at the adjacent Sandwell General Hospital, West Bromwich, were included in a prospective database. To be diagnosed with Barrett's and included in the database, patients had to have columnar-lined mucosa above the proximal margin of the gastric folds at endoscopy and evidence of intestinal metaplasia (IM) on biopsy.
Exclusion criteria	Patients who were diagnosed with OAC or high-grade dysplasia within 1 year of index endoscopy
Recruitment / selection of participants	All patients meeting inclusion criteria were included in the database.
Intervention(s)	Patients underwent endoscopic surveillance every 2 years until they reached 75 years of age or developed co-morbidity that, in the opinion of the responsible clinician, precluded further surveillance due to the risks of oesophagectomy. Quadrantic biopsies were taken every 2 cm throughout the Barrett's segment in addition to targeted biopsies of any focal lesions and reported by a gastrointestinal histopathologist.
Comparator	Patients failing to attend surveillance endoscopy despite being clinically indicated for surveillance.
Number of participants	431
Duration of follow-up	minimum 5 years
Indirectness	White light endoscopy not directly mentioned so downgraded for intervention indirectness.
Additional comments	The effects of surveillance were not adjusted for any of the potential confounders so there is likely to be considerable selection bias.

Study arms

Surveyed with endoscopy (N = 247)
Patients suitable for endoscopic surveillance and complied with surveillance (undergoing at least three endoscopies over at least 5 years of follow-up)

Failed to attend surveillance (N = 184)
Patients suitable for endoscopic surveillance but failed to attend for non-medical reasons (i.e. failed to attend or declined repeat endoscopy) and were not deceased

Characteristics

Study-level characteristics

Characteristic	**Study (N = 431)**
% Female No of events	n = 136 ; % = 31.55

Arm-level characteristics

Characteristic	**Surveyed with endoscopy (N = 247)**	**Failed to attend surveillance (N = 184)**
Age Median (IQR)	55.5 (51.2 to 66.6)	58 (49.2 to 63.6)

Outcomes

Study timepoints

- 5 year

Surveillance versus no surveillance

Outcome	Surveyed with endoscopy , 5 year, N = 247	Failed to attend surveillance, 5 year, N = 184
Death from OAC No of events	n = 11 ; % = 4.45	n = 9 ; % = 4.89
Progression to OAC No of events	n = 21 ; % = 8.5	n = 9 ; % = 4.89
All cause mortality No of events	n = 88 ; % = 35.62	n = 46 ; % = 25

Verbeek, 2014

Bibliographic Reference	Verbeek, R. E.; Leenders, M.; Ten Kate, F. J.; van Hillegersberg, R.; Vleggaar, F. P.; van Baal, J. W.; van Oijen, M. G.; Siersema, P. D.; Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study; American Journal of Gastroenterology; 2014; vol. 109 (no. 8); 1215-22

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	Not reported
Study type	Retrospective cohort study
Study location	Holland
Study setting	Secondary care - patients registered in Dutch Pathology Registry
Study dates	1999-2009
Sources of funding	No funding was received
Inclusion criteria	All patients diagnosed with OAC between 1999 and 2009 in the Netherlands were selected from the nationwide Netherlands Cancer Registry. Data were collected from the patient registration systems of all Dutch hospitals by trained personnel.
Exclusion criteria	Exclusion criteria were high-grade dysplasia, carcinoma in situ , and adenocarcinoma of the gastro-esophageal junction.

Recruitment / selection of participants	Retrospective cohort study: data were collected from the patient registration systems of all Dutch hospitals by trained personnel
Intervention(s)	All pathology reports related to the esophagus were obtained, including endoscopic evaluations with biopsies and resection specimens. Participation in an endoscopic surveillance program was defined as a prior Barrett's diagnosis 1 year or longer before OAC diagnosis with at least one additional endoscopy with biopsies between the first histologic Barrett's and OAC diagnosis. Adequate surveillance was defined as an interval between first Barrett's diagnosis and OAC diagnosis that was no more than 1.5 times longer than expected on the basis of diagnoses of intermediate histologic evaluations and recommended intervals in surveillance guidelines.
Comparator	The comparison group were people not given any surveillance.
Number of participants	671
Duration of follow-up	2 years
Indirectness	White light endoscopy was not described, so downgrading for intervention has been applied.
Additional comments	Cox regression analysis, adjusting for age, gender, time between BE and later OAC diagnosis, highest dysplasia grade before OAC, Hospital of diagnosis, tumour differentiation grade, tumour stage, resectability at diagnosis, and treatment.

Study arms

Adequate surveillance (N = 452)
Patients having adequate endoscopy (interval between first Barrett's diagnosis and OAC diagnosis that was no more than 1.5 times longer than expected on the basis of diagnoses of intermediate histologic evaluations and recommended intervals in surveillance guidelines, i.e., no more than 4.5 years in BE with no dysplasia, no more than 1.5 years in indefinite-for-dysplasia and low-grade dysplasia, and no more than 4.5 months in high-grade dysplasia). White Light Endoscopy was not described - instead endoscopy was described more generically, including biopsies and resection specimens. The intervention has therefore been downgraded for indirectness.

No surveillance (N = 219)
No endoscopic surveillance was given to this group. Reasons are unclear why surveillance not given, whether it was not indicated, or patients refused to attend.

Characteristics

Study-level characteristics

Characteristic	Study (N = 671)
% Female No of events	n = 162 ; % = 24.14

Arm-level characteristics

Characteristic	Adequate surveillance (N = 452)	No surveillance (N = 219)
Dysplasia grade before OAC of LGD or HGD No of events	n = 205 ; % = 45.35	n = 19 ; % = 8.67
Poorly differentiated tumour No of events	n = 107 ; % = 23.67	n = 71 ; % = 32.42
Tumour grade III or IV No of events	n = 94 ; % = 20.79	n = 94 ; % = 42.92

Outcomes

Study timepoints

- 2 year

Surveillance versus no surveillance

Outcome	Adequate surveillance vs No surveillance, 2 year, N2 = 219, N1 = 452
Mortality from OAC Hazard ratio/95% CI	0.79 (0.62 to 0.92)

Adjusted HR: 0.79 (0.62-0.92)

Surveillance versus no surveillance

Outcome	Adequate surveillance, 2 year, N = 452	No surveillance, 2 year, N = 219
Progression to type IV tumour stage No of events	n = 42 ; % = 9	n = 62 ; % = 28

Appendix E – Forest plots

Surveillance versus no surveillance

Figure 2: Mortality from OAC (adjusted HR)

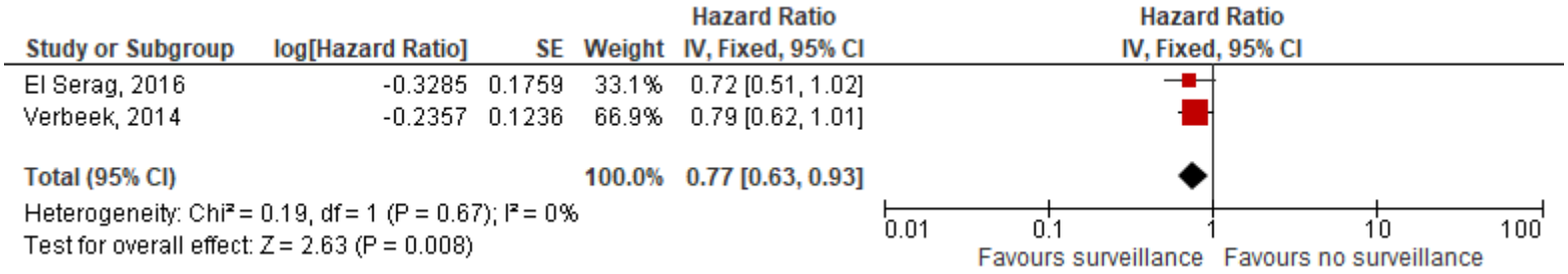


Figure 3: Mortality from OAC (adjusted OR)

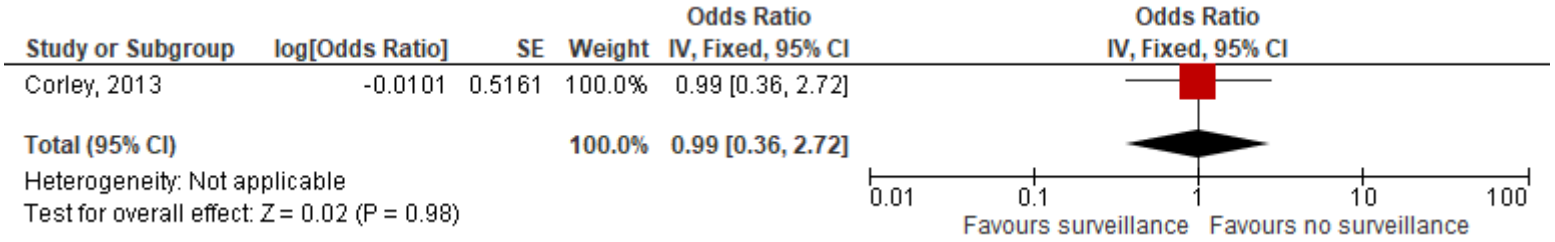


Figure 4: Mortality from OAC (unadjusted RR)

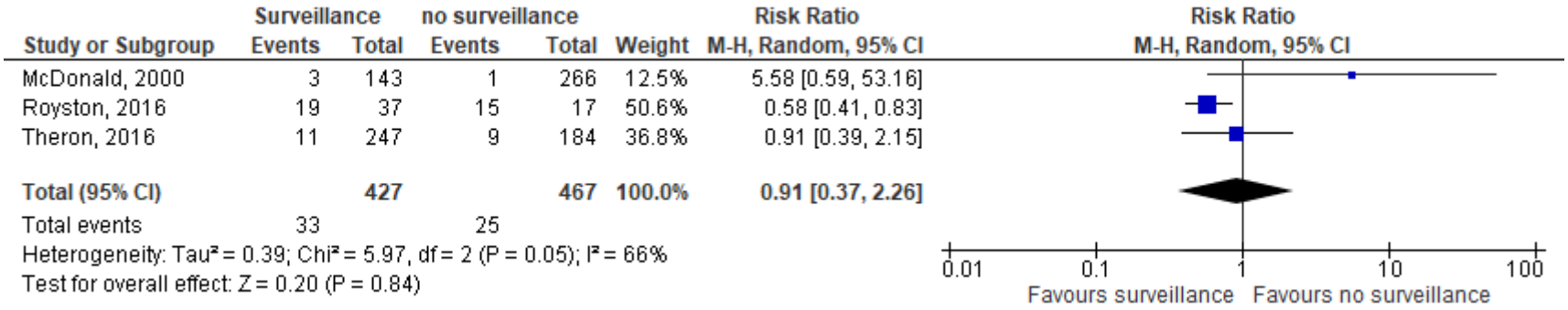


Figure 5: All cause mortality (adjusted HR)

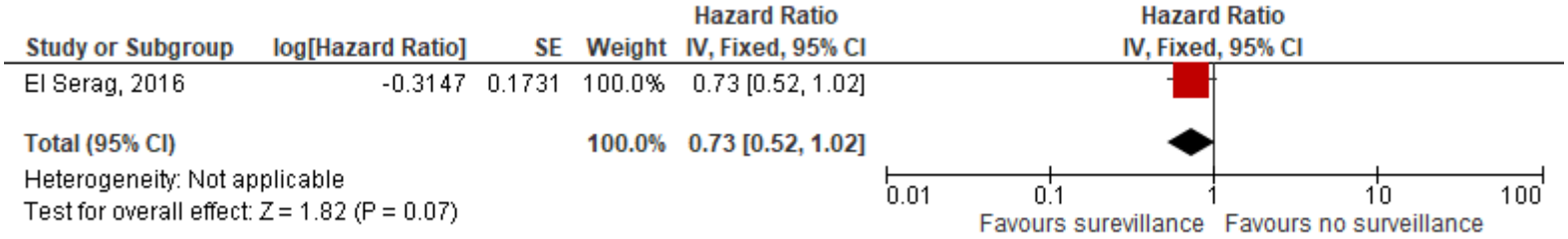


Figure 6: All cause mortality (anadjusted RR)

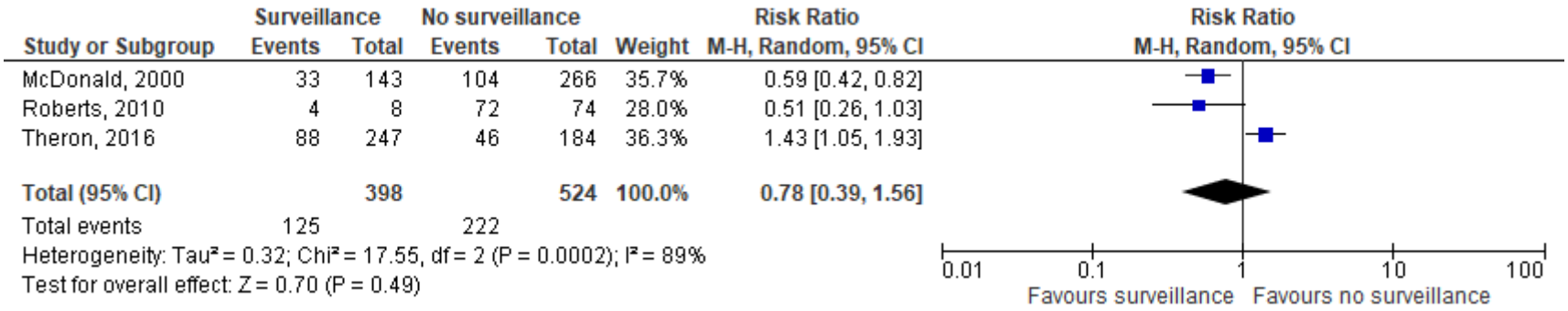


Figure 7: Progression to OAC (unadjusted RR)

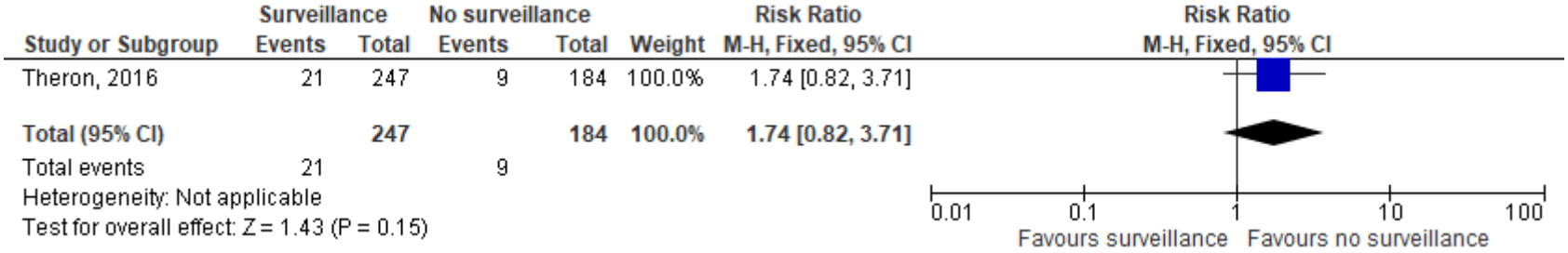
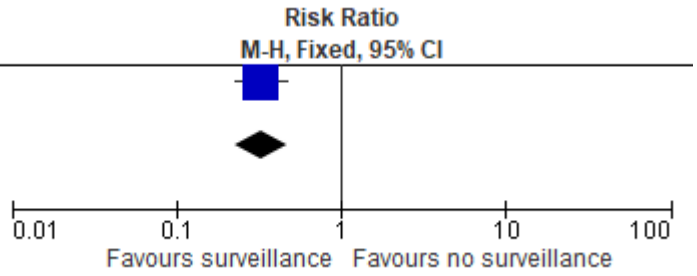


Figure 8: Progression to Type IV tumour stage (unadjusted RR)

Study or Subgroup	Surveillance Events	Surveillance Total	No surveillance Events	No surveillance Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Verbeek, 2014	42	452	62	219	100.0%	0.33 [0.23, 0.47]
Total (95% CI)		**452**		**219**	**100.0%**	**0.33 [0.23, 0.47]**
Total events	42		62			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.12 (P < 0.00001)



Appendix F – GRADE tables

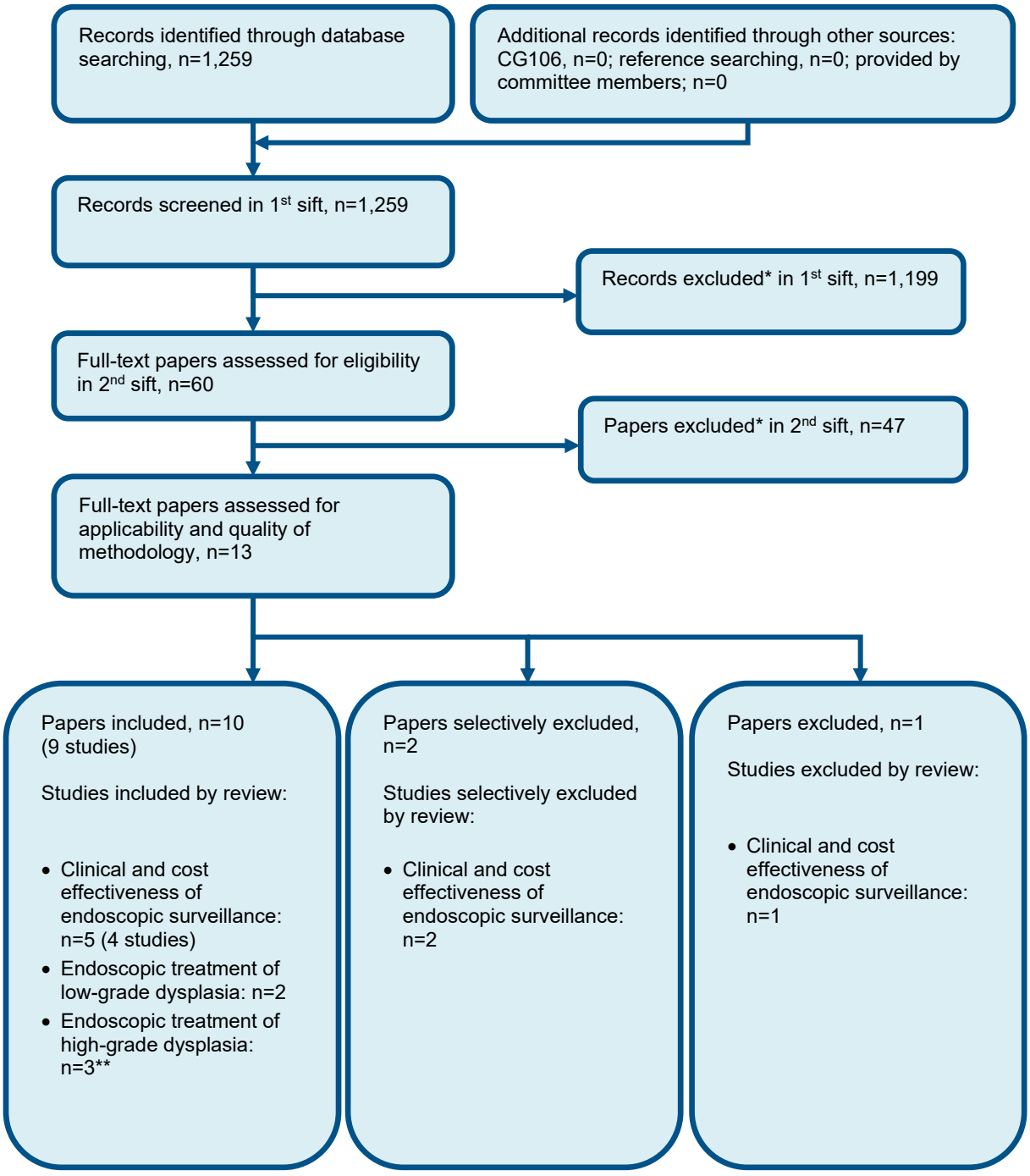
Table 7: Clinical evidence profile: surveillance versus no surveillance

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	surveillance	No surveillance	Relative (95% CI)	Absolute		
Mortality from OAC at 2-5 years (adjusted hazard ratios)												
2	Observational studies	Serious risk of bias[1]	no serious inconsistency[2]	none	Serious imprecision[3]	none	661	434	HR 0.77 (0.63, 0.93)	-	LOW	CRITICAL
Mortality from OAC at 3 years (adjusted odds ratios)												
1	Observational studies	Serious risk of bias[1]	NA	none	Very serious imprecision[3]	none	82	57	OR 0.99 (0.36, 2.72)	-	VERY LOW	CRITICAL
Mortality from OAC at 3-10 years (risk ratios)												
3	Observational studies	Very serious risk of bias[1]	Serious inconsistency[2]	none	Very serious imprecision[3]	none	33/427 (7.7%)	25/467 (5.4%)	Random effects RR 0.91 (0.37, 2.26)	4 fewer per 1000 (from 31 fewer to 62 more)	VERY LOW	CRITICAL
All cause mortality at 5 years (adjusted hazard ratios)												
1	Observational studies	Serious risk of bias[1]	NA	none	Serious imprecision[3]	none	209	215	HR 0.73 (0.52, 1.02)	-	VERY LOW	CRITICAL
All cause mortality at 5-10 years (risk ratios)												
3	Observational studies	Very serious risk of bias[1]	Very serious inconsistency[2]	none	Very serious imprecision[3]	none	125/398 (31.4%)	222/524 (42.4%)	Random effects RR: 0.78 (0.39, 1.56)	86 fewer per 1000 (from 239	VERY LOW	CRITICAL

										fewer to 219 more)		
Progression to OAC at 5 years												
1	Observational studies	Very serious risk of bias[1]	NA	none	Serious imprecision[3]	none	21/247 (8.5%)	9/184 (4.9%)	RR: 1.74 (0.82, 3.71)	36 more per 1000 (from 9 fewer to 133 more)	VERY LOW	CRITICAL
Progression to type IV tumour stage												
1	Observational studies	Very serious risk of bias[1]	NA	none	none	none	42/452 (9.3%)	62/219 (28.3%)	RR: 0.33 (0.23, 0.47)	190 fewer per 1000 (from 150 fewer to 218 fewer)	LOW	CRITICAL

[1] Downgraded by one increment if moderate risk of bias and downgraded by two increments if serious or critical risk of bias
[2] Downgraded by two increments because of very serious heterogeneity (I^2 > 75%)
[3] Downgraded by one increment if the 95% CIs crossed one of the default MIDs (0.8 or 1.25) and downgraded by two increments if the 95% CIs crossed both of the default MIDs (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 – Economic evidence tables

Study	Garside 2006[7], Somerville 2008[19]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic Markov model based on systematic review of case series **Approach to analysis:** Modelled natural history of BO in a cohort who have had an initial diagnosis of BO at endoscopy with or without dysplasia. Progressive health states include LGD, HGD and OA. **Perspective:** UK NHS **Follow-up:** 20 years **Discounting:** Costs: 6%; Outcomes: 1.5%	**Population:** Patients with BO **Cohort settings:** Start age: 55 Male: 100% **Intervention 1:** No surveillance **Intervention 2:** Endoscopic surveillance and biopsy at 3-yearly intervals for ND BO, yearly intervals for LGD, and 3-monthly for HGD.	**Total costs (mean per patient):** Intervention 1: £2,951 Intervention 2: £3,869 Incremental (2−1): £918 (95% CI: NR; p=NR) **Currency & cost year:** 2004 UK pounds **Cost components incorporated:** Pharmacological management, endoscopy (including biopsy), presurgical tests, surgical treatment of OA, treatment of complications from surgical treatment of OA, cost of untreatable OA	**QALYs (mean per patient):** Intervention 1: 12.03 Intervention 2: 11.98 Incremental (2−1): -0.048 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Dominated (pa) 95% CI: Probability Intervention 2 cost effective (£30K threshold): 11% Probability Intervention 2 dominated: 75% **Analysis of uncertainty:** The model results were most sensitive to the recurrence rate of adenocarcinoma after oesophagectomy, the rate at which adenocarcinoma becomes symptomatic and the various health state utility scores, which all resulted in a cost per QALY below £30,000 per QALY gained.

Data sources
Health outcomes: In the absence of RCT data, data from a systematic review of case series were used to estimate transition probabilities between health states. Incidence per patient year of follow-up was used as annual progression rates from BO through each dysplastic state to OA and assumed to be the same in each year. As the case series listed only the diagnosis at the final endoscopy, it was assumed that patients progress sequentially through dysplastic states of increasing severity. **Quality-of-life weights:** No robust utility values for the health states associated with BO were found in the literature, so utility estimates were instead obtained from the NHS Value of Health Panel, whose members are trained to use standard gamble techniques to express preferences. **Cost sources:** Cost of proton pump inhibitors were taken from the British National Formulary No.47 (March 2004). All other costs were taken from the 2002 NHS reference costs and inflated to 2004 costs using Health Service Cost Index estimates.
Comments
Source of funding: Health Technology Assessment Programme (project number 03/49/01). **Limitations:** Discounting for costs and outcomes were not in line with the current NICE reference case. The health outcomes were derived from case series. QALYs were not captured using the EQ-5D. The model includes complications associated with oesophagectomy, but not those associated with endoscopy. Costs are from dated sources and may no longer reflect costs associated with current care in the NHS. **Other:**
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; BO= Barrett's oesophagus; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; LGD= low-grade dysplasia; ND= no dysplasia; NR= not reported; OA= oesophageal adenocarcinoma; pa= probabilistic analysis; QALYs= quality-adjusted life years; RCT= randomised controlled trial

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Gordon 2014[8]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** 10-state probabilistic Markov model based on observational studies. **Approach to analysis:** The model used data from large epidemiological studies and surveillance based on the Seattle protocol. Of the hypothetical cohort, 95% entered the model with a diagnosis of ND BO, 4% with LGD and 1% with HGD. **Perspective:** Australian NHS (Medicare) **Follow-up:** 30 years **Discounting:** Costs & Outcomes: 5%	**Population:** Patients with non-dysplastic BO **Cohort settings:** Start age: 50 Male: NR **Intervention 1:** No surveillance **Intervention 2:** 2-yearly endoscopic surveillance of patients with ND BO and 6-monthly surveillance of patients with LGD **Intervention 3:** Biomarker-modified endoscopic surveillance strategy (hypothetical)	**Total costs (mean per patient):** Incremental (2−1): £4,408 (95% CI: NR; p=NR) Incremental (3−1): £2,739 (95% CI: NR; p=NR) **Currency & cost year:** 2011 US dollars, where costs were first inflated to 2011 AU dollars, then converted to US dollars (AUD 1= USD 1), (presented here as 2011 UK pounds[(a)]) **Cost components incorporated:** Resource use included biopsies, ultrasounds, imaging, endoscopic treatments and investigations, hospitalisations, in-hospital AEs, chemotherapy, radiotherapy, monitoring, stents and palliative care.	**QALYs (mean per patient):** Incremental (2−1): 0.16 (95% CI: NR; p=NR) Incremental (3−1): 0.15 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £28,436 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective versus no surveillance (£46.7K threshold): 16% **ICER (Intervention 3 versus Intervention 1):** £17,899 per QALY gained (pa) 95% CI: NR Probability Intervention 3 cost effective versus no surveillance (£46.7K threshold): 61% **Analysis of uncertainty:** Results from one-way sensitivity analyses showed that annual progression rates from ND BO to HGD and from LGD to HGD were most sensitive to changes in the cost per QALY. A strategy of less frequent surveillance endoscopies also improved cost effectiveness (see table below). Surveillance frequency / ICER ND BO 3 yrs/LGD 6 months: £22,516 ND BO 5 yrs/LGD 6 months: £17,831 ND BO 3 yrs/LGD annual: £14,838 ND BO none/LGD annual: £4,718

Data sources
Health outcomes: The natural history of BO was taken from large observational studies,[1, 3, 9] while progression of non-dysplastic BO to adenocarcinoma was taken from a meta-analysis. The risk of progression in the biomarker-modified surveillance arm was based on the outcomes reported in Galipeau 2007.[6] Transition rates to dysplasia and cancer were generated by using an expectation-maximisation algorithm based on positive and negative biomarker results. **Quality-of-life weights:** EQ-5D: background utility value was reported using the Australian QoL preferences, while disutilities were taken from the literature and mostly based on EQ-5D UK tariff. **Cost sources:** Resources were valued using national price schedules and public hospital clinical costs for inpatient surgical stays. Costs for the diagnosis, treatment and follow-up of oesophageal cancer were taken from patient-level data from the Australian Cancer Study (ACS).
Comments
Source of funding: NR. **Limitations:** The Australian perspective is not in line with the NICE reference case. Costs and outcomes were not discounted in line with the NICE reference case. Progression rates of BO were taken from observational studies. EQ-5D was valued using the Australian tariff. Model results were based on a 90% attendance rate for surveillance appointments, which was not tested during sensitivity analysis. Only patients with confirmed IM were included in the analysis, and since BSG guidelines do not require the presence of IM for the diagnosis of BO, the results are unlikely to be applicable to UK practice. **Other:**
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: AE= adverse event; BSG= British Society of Gastroenterology; BO= Barrett's oesophagus; 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HGD= high-grade dysplasia; ICER= incremental cost-effectiveness ratio; IM= intestinal metaplasia; LGD= low-grade dysplasia; ND= non-dysplasia; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) Converted using 2011 purchasing power parities [16]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

<table>
<tr><th>Study</th><th colspan="4">Lindblad 2017[12]</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)

Study design: Adapted Markov model from Gordon 2014.
Approach to analysis: To determine the cost effectiveness of limiting surveillance to higher-risk individuals. Patients were excluded if:
1. They had a CLO segment of <2cm and no dysplasia at index endoscopy.
2. They did not have IM identified histologically in either of the first two endoscopies.

Perspective: Australian NHS (Medicare)
Follow-up: 30 years

Discounting: Costs & Outcomes: 5%</td>
<td>Population:
Patients with a CLO who were enrolled in a BO surveillance program.

Cohort settings:
Start age: 50
Male: 67%

Intervention 1:
No surveillance

Intervention 2:
Endoscopic surveillance in line with the Seattle protocol (2-yearly endoscopy in patients with known CLE, increased to 6-monthly in those with LGD.</td>
<td>Total costs (mean per patient):
Intervention 1: £11,360
Intervention 2: £4,236
Incremental (2−1): £7,126
(95% CI: NR; p=NR)

Currency & cost year:
NR (but assumed to be the same as was reported in Gordon 2014 (presented here as 2011 UK pounds[(a)])

Cost components incorporated:
NR (but since the model was adapted from Gordon 2014, it is assumed to be what was reported there).</td>
<td>QALYs (mean per patient):
Intervention 1: 11.582
Intervention 2: 12.033
Incremental (2−1): 0.451
(95% CI: NR; p=NR)</td>
<td>ICER (Intervention 2 versus Intervention 1):
£15,797 per QALY gained (pa)
95% CI: NR
Probability Intervention 2 cost effective (£23.4K threshold): 63%

Analysis of uncertainty: Scenario analysis explored the effect of excluding further patients from surveillance based on the length of the CLE segment. The costs per QALY when limiting surveillance to patients with a CLE length of less than 3cm was £16,721, and £51,671 when it was limited to patients with a CLE length of less than 4cm.
<table>
<tr><th></th><th colspan="2">Probability Intervention 2 cost effective at threshold</th></tr>
<tr><th></th><th>£20k</th><th>£30k</th></tr>
<tr><td>BO <2cm length</td><td>58%</td><td>67%</td></tr>
<tr><td>BO <3cm length</td><td>48%</td><td>55%</td></tr>
<tr><td>BO <4cm length</td><td>40%</td><td>45%</td></tr>
</table>
</td>
</tr>
<tr><th colspan="5">Data sources</th></tr>
<tr><td colspan="5">Health outcomes: Transition probabilities between health states were either calculated from the Barrett’s oesophagus surveillance program or taken from Gordon 2014.[8] Quality-of-life weights: Derived from South Australian data where possible, and then published literature. Cost sources: Derived from South Australian data where possible, and then published literature.</td></tr>
</table>

Comments
Source of funding: None declared. **Limitations:** The Australian perspective is not in line with the NICE reference case. Costs and outcomes were not discounted in line with the NICE reference case. The sources for costs and utilities were not clearly defined. **Other:**
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: BO= Barrett's oesophagus; BSG= British Society of Gastroenterology; 95% CI= 95% confidence interval; CLO= columnar-lined oesophagus; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; IM= intestinal metaplasia; LGD= low-grade dysplasia; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) Converted using 2011 purchasing power parities [16]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Omidvari 2020[15]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: CUA (health outcome: QALYs)

Study design: Microsimulation model

Approach to analysis: Costs and QALYs resulting from surveillance according to the Dutch guidelines was compared to a no surveillance strategy.

Perspective: Dutch NHS

Follow-up: lifetime

Discounting: Costs & Outcomes: 3%

Population:
Patients with BO

Cohort settings:
Start age: 60
Male: NR

Intervention 1:
No surveillance

Intervention 2:
Surveillance according to Dutch guidelines (ND short-segment BO: 5 years, ND long-segment BO: 3 years, LGD: 6 months & 1 year)

Intervention 3: Intensive NDBO & LGD (ND short-segment BO: 3.5 years, ND long-segment BO: 2 years, LGD: 3 months & 6 months)

Intervention 4: Intensive NDBO (ND short-segment BO: 3.5 years, ND long-segment BO: 2 years, LGD: 6 months & 1 year)

Intervention 5: Intensive LGD (ND short-segment BO: 5 years, ND long-segment BO: 3 years, LGD: 3 months & 6 months)

Intervention 6: Very intensive NDBO & LGD (ND short-segment BO: 2 years, ND long-segment BO: 1 year, LGD: 3 months & 6 months)

Int.	Total costs (mean per patient)	Total QALYs (mean per patient)	Inc. cost	Inc. QALYs	Cost per QALY
1	NR	NR			-
2	NR	NR	£4,381	0.333	£13,156
5	NR	NR	£526	0.006	ED
4	NR	NR	£1,402	0.028	£50,071
3	NR	NR	£789	0.005	ED
7	NR	NR	£2,454	0.023	£106,696
6	NR	NR	£1,051	0.009	£116,778

Total costs (mean per patient):
Incremental
2−1: £4,381
3−1: £6,572
4−1: £5,783
5−1: £4,907
6−1: £9,288
7−1: £8,237
(95% CI: NR; p=NR)

Currency & cost year:
Mostly 2017 Euros (presented here as 2017 UK pounds[(a)])

Cost components incorporated:

QALYs (mean per patient):
Incremental
2−1: 0.333
3−1: 0.366
4−1: 0.361
5−1: 0.339
6−1: 0.393
7−1: 0.384
(95% CI: NR; p=NR)

Cost per QALY gained (da)
2 versus 1: £13,156
3 versus 1: £17,956
4 versus 1: £16,019
5 versus 1: £14,475
6 versus 1: £23,634
7 versus 1: £21,451
95% CI: NR

Analysis of uncertainty: The results were robust to changes to the age of the cohort, the progression rate of Barrett's oesophagus and participation rates for surveillance.

	Intervention 7: Very intensive NDBO (ND short-segment BO: 2 years, ND long-segment BO: 1 year, LGD: 6 months & 1 year)	Cost of endoscopy, initial EET treatment plus follow up costs and those resulting from complications, annual outpatient visits after oesophagectomy and care for stages 1-4 OA.		
Data sources				
Health outcomes: Progression rate of BO were taken from the PROBAR observational multicentre prospective study (median follow-up time of 8 years).[11] Incidence rates of OA were based on those observed in the Dutch population between 2012 to 2017.[10] **Quality-of-life weights:** Utilities/disutilities were taken from literature and expert feedback **Cost sources:** Resource use utilisation was based on a retrospective chart review at Erasmus MC University Medical Centre. Unit costs based on average prices from all hospitals in The Netherlands (National Healthcare Institute of The Netherlands).				
Comments				
Source of funding: Dutch Cancer Society, grant number: EMRC 2014-7222. **Limitations:** A UK perspective was not used in the analysis, and the study is therefore not in line with the NICE reference case. QALYs were not captured using the EQ-5D. Costs and outcomes were not discounted in line with the NICE reference case. Longer term outcomes of EET were extrapolated in the absence of evidence. **Other:** It was assumed that all patients attended all surveillance and treatment sessions and that surveillance stopped at 80 years.				
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations				

Abbreviations: BO= Barrett's oesophagus; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; ED= extendedly dominated; EET: endoscopic eradication therapy; EQ-5D= Euroqol 5 dimensions LGD= low-grade dysplasia; ND= non dysplasia; NDBO= non-dysplastic Barrett's oesophagus; NHS= national health service; OA= oesophageal adenocarcinoma; NR= not reported; QALYs= quality-adjusted life years

(a) Converted using 2017 purchasing power parities [16]

(b) Directly applicable / Partially applicable / Not applicable

(c) *Minor limitations / Potentially serious limitations / Very serious limitations*

Appendix I – Excluded studies

Clinical studies

Table 8: Studies excluded from the clinical review

Study	Reason for exclusion
Areia, M., Carvalho, R., Cadime, A. T. et al. (2013) Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. Helicobacter 18(5): 325-37	- Population not relevant to this review protocol
Areia, M.; Dinis-Ribeiro, M.; Rocha Goncalves, F. (2014) Cost-utility analysis of endoscopic surveillance of patients with gastric premalignant conditions. Helicobacter 19(6): 425-36	- Study design not relevant to this review protocol - Population not relevant to this review protocol
Barbiere, J. M. and Lyratzopoulos, G. (2009) Cost-effectiveness of endoscopic screening followed by surveillance for Barrett's oesophagus: a review. Gastroenterology 137(6): 1869-76	- Systematic review used as source of primary studies
Bennett, C., Moayyedi, P., Corley, D. A. et al. (2015) BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett's Oesophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia. American journal of gastroenterology 110(5): 662-82; quiz 683	- Study design not relevant to this review protocol
Bennett, C, Green, S, DeCaestecker, J et al. (2020) Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Bhat, S. K., McManus, D. T., Coleman, H. G. et al. (2015) Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study. Gut 64(1): 20-5	- Interventions in study did not match protocol interventions. The study interventions were known Barretts diagnosis versus unknown Barretts diagnosis. Only 78% in the known Barretts diagnosis group had received surveillance, making the groups incongruent with those of the protocol. Furthermore it was unclear if all patients in the study had Barretts.
Codipilly, D. C., Chandar, A. K., Singh, S. et al. (2018) The Effect of Endoscopic Surveillance in Patients With Barrett's Oesophagus: A Systematic Review and Meta-analysis. Gastroenterology 154(8): 2068-2086.e5	- Systematic review used as source of primary studies
Connor, M. J. and Sharma, P. (2003) Chromoendoscopy and magnification endoscopy in Barrett's oesophagus. Gastrointestinal endoscopy clinics of North America 13(2): 269-277	- Review article but not a systematic review
Cooper, G. S., Yuan, Z., Chak, A. et al. (2002) Association of prediagnosis endoscopy with stage and survival in adenocarcinoma of the oesophagus and gastric cardia. Cancer 95(1): 32-8	- Unclear if all patients in study had Barretts

Study	Reason for exclusion
Craanen, M. E., Blok, P., Meijer, G. A. et al. (2002) Surveillance in Barrett's oesophagus: a critical reappraisal. Scandinavian Journal of Gastroenterology - Supplement: 4-8	- Review article but not a systematic review
di Pietro, M.; Canto, M. I.; Fitzgerald, R. C. (2018) Endoscopic Management of Early Adenocarcinoma and Squamous Cell Carcinoma of the Oesophagus: Screening, Diagnosis, and Therapy. Gastroenterology 154(2): 421-436	- Review article but not a systematic review
Ding, Y. E., Li, Y., He, X. K. et al. (2018) Impact of Barrett's oesophagus surveillance on the prognosis of oesophageal adenocarcinoma: A meta-analysis. Journal of digestive diseases 19(12): 737-744	- Systematic review used as source of primary studies
Garside, R., Pitt, M., Somerville, M. et al. (2006) Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. Health Technology Assessment (Winchester, England) 10(8): 1-142, iii	- Systematic review used as source of primary studies
Gindea, C., Birla, R., Hoara, P. et al. (2014) Surveillance in Barrett oesophagus. Journal of medicine and life 73: 61-67	- Review article but not a systematic review
Gordon, L. G. and Mayne, G. C. (2013) Cost-effectiveness of Barrett's oesophagus screening and surveillance. Best Practice & Research in Clinical Gastroenterology 27(6): 893-903	- Review article but not a systematic review
Grant, K. S., DeMeester, S. R., Kreger, V. et al. (2013) Effect of Barrett's oesophagus surveillance on oesophageal preservation, tumor stage, and survival with oesophageal adenocarcinoma. Journal of Thoracic and Cardiovascular Surgery 146(1): 31-7	- Unclear if all patients in study had Barretts
Grover, M., Strickland, C., Kesler, E. et al. (2006) How should patients with Barrett's oesophagus be monitored?. Journal of Family Practice 55(3): 243-7	- Review article but not a systematic review
Hirst, N. G., Gordon, L. G., Whiteman, D. C. et al. (2011) Is endoscopic surveillance for non-dysplastic Barrett's oesophagus cost-effective? Review of economic evaluations. Journal of Gastroenterology & Hepatology 26(2): 247-54	- Systematic review used as source of primary studies
Kastelein, F., van Olphen, S. H., Steyerberg, E. W. et al. (2016) Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. Gut 65(4): 548-54	- Unclear if all patients in study had Barretts single cohort
Li, F., Li, X., Guo, C. et al. (2019) Estimation of Cost for Endoscopic Screening for Oesophageal Cancer in a High-Risk Population in Rural China: results from a Population-Level Randomized Controlled Trial. PharmacoEconomics 37(6): 819-827	- Study design not relevant to this review protocol

Study	Reason for exclusion
Luo, H., Xu, G., Li, C. et al. (2019) Real-time artificial intelligence for detection of upper gastrointestinal cancer by endoscopy: a multicentre, case-control, diagnostic study. The lancet. Oncology 20(12): 1645-1654	- Study design not relevant to this review protocol
Old, O. J.; Almond, L. M.; Barr, H. (2015) Barrett's oesophagus: how should we manage it?. Frontline gastroenterology 6(2): 108-116	- Systematic review used as source of primary studies
Provenzale, D., Kemp, J. A., Arora, S. et al. (1994) A guide for surveillance of patients with Barrett's oesophagus. American journal of gastroenterology 89(5): 670-80	- Study design not relevant to this review protocol
Qiao, Y., Hyder, A., Bae, S. J. et al. (2015) Surveillance in Patients With Barrett's Oesophagus for Early Detection of Oesophageal Adenocarcinoma: A Systematic Review and Meta-Analysis. Clinical and Translational Gastroenterology 6: e131	- Systematic review used as source of primary studies
Rastogi, A., Puli, S., El-Serag, H. B. et al. (2008) Incidence of oesophageal adenocarcinoma in patients with Barrett's oesophagus and high-grade dysplasia: a meta-analysis. Gastrointestinal endoscopy 67(3): 394-8	- Study does not contain an intervention relevant to this review protocol
Rubenstein, J. H. and Inadomi, J. M. (2021) Cost-Effectiveness of Screening, Surveillance, and Endoscopic Eradication Therapies for Managing the Burden of Oesophageal Adenocarcinoma. Gastrointestinal endoscopy clinics of North America 31(1): 77-90	- Study does not contain an intervention relevant to this review protocol
Rubenstein, J. H., Sonnenberg, A., Davis, J. et al. (2008) Effect of a prior endoscopy on outcomes of oesophageal adenocarcinoma among United States veterans. Gastrointestinal endoscopy 68(5): 849-55	- Unclear if all patients in study had Barretts
Sampliner, R. E. (2010) Surveillance of Barrett's oesophagus. Techniques in Gastrointestinal Endoscopy 12(2): 67-68	- Review article but not a systematic review
Sayana, H.; Wani, S.; Sharma, P. (2007) Oesophageal adenocarcinoma and Barrett's oesophagus. Minerva gastroenterologica e dietologica 53(2): 157-169	- Review article but not a systematic review
Shaheen, N. J.; Provenzale, D.; Sandler, R. S. (2002) Upper endoscopy as a screening and surveillance tool in oesophageal adenocarcinoma: a review of the evidence. American journal of gastroenterology 97(6): 1319-27	- Systematic review used as source of primary studies
Singh, R.; Ragunath, K.; Jankowski, J. (2007) Barrett's Oesophagus: Diagnosis, Screening, Surveillance, and Controversies. Gut & Liver 1(2): 93-100	- Review article but not a systematic review
Smith, A. M., Maxwell-Armstrong, C. A., Welch, N. T. et al. (1999) Surveillance for Barrett's oesophagus in the UK. British journal of surgery 86(2): 276-280	- Study design not relevant to this review protocol

Study	Reason for exclusion
Spechler, S. J. (2013) Barrett oesophagus and risk of oesophageal cancer: a clinical review. Jama 310(6): 627-36	- Review article but not a systematic review
Tramontano, A. C., Sheehan, D. F., Yeh, J. M. et al. (2017) The Impact of a Prior Diagnosis of Barrett's Oesophagus on Oesophageal Adenocarcinoma Survival. American Journal of Gastroenterology 112(8): 1256-1264	Unclear if all patients in study had Barretts
van Sandick, J. W., van Lanschot, J. J., Kuiken, B. W. et al. (1998) Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 43(2): 216-22	- Data not reported in an extractable format or a format that can be analysed
Wong, T.; Tian, J.; Nagar, A. B. (2010) Barrett's surveillance identifies patients with early esophageal adenocarcinoma. American Journal of Medicine 123(5): 462-7	- Comparator in study does not match that specified in this review protocol [Not all in the comparator group had Barrett's oesophagus]
Yang, S, Wu, S, Huang, Y et al. (2012) Screening for oesophageal cancer. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Yang, Y., Chen, H. N., Wang, R. et al. (2015) Cost-Effectiveness Analysis on Endoscopic Surveillance Among Western Patients With Barrett's Oesophagus for Oesophageal Adenocarcinoma Screening. Medicine 94(39): e1105	- Study design not relevant to this 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.

Table 9: Studies excluded from the health economic review

Reference	Reason for exclusion
Furneri 2019 [5]	This study was a cost-consequences analysis. Given that there were cost-utility analyses in the review, it was selectively excluded.
Roberts 2010[17]	This study was a cost effectiveness analysis. Given that there were cost-utility analyses in the review, it was selectively excluded.
Yang 2015[22]	Excluded as rated not applicable. The study perspective was generalised to the Western perspective, while costs were from the US healthcare setting.