National Institute for Health and Care Excellence

Draft for consultation

Vitamin B12 deficiency in over 16s: diagnosis and management

[G] Evidence review for monitoring for gastric cancer in people with vitamin B12 deficiency due to autoimmune gastritis

NICE guideline <number>

Evidence reviews underpinning recommendations 1.7.1 and 1.7.2 and the research recommendation in the NICE guideline

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Draft for Consultation

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Contents

1 Monitoring for gastric cancer in people with vitamin B12 deficiency due to autoimmune gastritis

1.1 Review question

What monitoring should be offered to people with pernicious anaemia to identify gastric cancer?

1.1.1 Introduction

Intrinsic factor is essential for the normal absorption of vitamin B12. Intrinsic factor is produced by the parietal cells of the stomach. Inflammatory conditions of the stomach, predominantly autoimmune gastritis and less commonly H. pylori infection, can lead to the dysfunction and the eventual loss of parietal cells in the stomach, resulting in vitamin B12 deficiency. Previous studies have suggested that several types of cancer affecting the cells of the stomach may be more likely to occur in some people who have vitamin B12 deficiency. This increased risk of stomach cancer development is not due to the vitamin B12 deficiency itself, but the associated stomach inflammation. The two main types of stomach cancer involved are gastric adenocarcinomas and gastric neuroendocrine tumours. The increased risk is therefore only found in those patients who have a gastric cause of vitamin B12 deficiency. This association is plausible given that both the chronic inflammation and the physiological changes such as reduced gastric acid secretion are possible risk factors for stomach cancer development.

The overall risk of cancers affecting the stomach in people with autoimmune gastritis is uncertain. There is no standardised approach to screening and surveillance of the stomach for cancers. The yield and clinical benefit of such screening, as well as the optimal methodology and frequency of monitoring, have not been previously defined.

This review seeks to assess the most clinically and cost-effective monitoring strategy to identify gastric cancer in people with vitamin B12 deficiency due to autoimmune gastritis, including the type of procedures and frequency.

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 with diagnosed pernicious anaemia (diagnosis as defined by the studies) Exclusion: other types/causes of vitamin B12 deficiency Strata: Other risk factors for gastric cancer (patients with any previous gastric surgery, including bariatric surgery)
Interventions	• Monitoring for gastric cancer: ○ Gastroscopy ○ Barium meal ○ Pepsinogen (followed by gastroscopy for those at high risk) ○ Gastrin (followed by gastroscopy for those at high risk)

	○ Combined pepsinogen + gastrin (followed by gastroscopy for those at high risk) ○ 3 staged pepsinogen, followed by gastrin (followed by gastroscopy for those at high risk) ○ 3 staged gastrin, followed by pepsinogen (followed by gastroscopy for those at high risk) Stratify by: Frequency
Comparisons	• All monitoring strategies compared with each other (what is included and frequency of monitoring) • No monitoring
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality • Quality of life • Diagnosis of cancer • Stage of cancer at diagnosis/surgical resectability • Incidence of gastric neuroendocrine tumours (AKA carcinoid tumours/NETS/NENS) • Adverse events (procedure related): ○ bleeding ○ perforation ○ aspiration
Study design	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered) Key confounders: previous gastric surgery Published NMAs and IPDs will be considered for inclusion.

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

A search was conducted for randomised trials comparing the effectiveness of monitoring strategies with each other or with no monitoring for gastric cancer in people with pernicious anaemia. No randomised trials were identified that included people with pernicious anaemia only. One randomised controlled trial[2] comparing gastroscopic follow up at 24 months with gastroscopic follow up at 48 months in people with atrophic gastritis was identified. 59.5% of study participants had pernicious anaemia and were therefore considered an indirect population and evidence was downgraded. The study is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 4).

As no direct evidence from randomised trials was identified, a search was conducted for non-randomised studies. Two cohort studies[1, 6] comparing gastroscopy with no monitoring were included. The studies are summarised in Table 3 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 5 and 6).

None of the included studies reported whether participants had undergone previous gastric surgery. Evidence was identified for mortality, incidence of carcinoid tumours and gastric carcinoma. No evidence was identified for quality of life, stage of cancer at diagnosis/surgical resectability or adverse events.

No evidence was identified for the effectiveness of barium meal, pepsinogen (followed by gastroscopy for those at high risk), gastrin (followed by gastroscopy for those at high risk), combined pepsinogen + gastrin (followed by gastroscopy for those at high risk), 3 staged pepsinogen, followed by gastrin (followed by gastroscopy for those at high risk), or 3 staged gastrin, followed by pepsinogen (followed by gastroscopy for those at high risk).

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 J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of randomised controlled trials included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Lahner 2001[2]	**Gastroscopy at 24 months** *N=30* Invited to undergo follow-up at a median of 24 months (range 20-26 months) after diagnosis of body-predominant atrophic gastritis Versus **Gastroscopy at 48 months** *N=31*	Outpatients with body-predominant atrophic gastritis recruited in a screening program for early detection of BAG in patients with unexplained anaemia or long-standing dyspepsia. 59.5% had pernicious anaemia.	At 2 vs. 4 years: Carcinoid tumours	Criteria for diagnosis of body–predominant atrophic gastritis: fasting gastrin above upper normal values, hypochlorhydria/achlorhydria to pentagastrin stimulation, and histologic confirmation of gastric body mucosal atrophy. Criteria for diagnosis of pernicious

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up scheduled at a median of 48 months (range 38-60 months)	Population strata (previous gastric surgery): not reported Age: group A median (range) 55.5 (22-68) years, group B 59.5 (28-73) years Sex: 15 males, 27 females		anaemia: macrocytic anaemia (haemoglobin levels less than 14 g/dL for men and less than 12 g/dL for women; mean corpuscular volume greater than 100 fL), vitamin B12 levels less than 220 pg/mL (normal range 220 to 1130 pg/mL), recovery from anaemia after treatment with intramuscular vitamin B12, hypochlorhydria/achlorhydria to pentagastrin stimulation, and histologic confirmation of gastric body mucosa atrophy. Conducted in Italy

Table 3: Summary of non-randomised studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Armbrecht 1990 [1]	**Gastroscopy** *N= 12* Histories of clinical symptoms taken and upper gastrointestinal endoscopies performed at a mean interval of 14 months Versus **No monitoring** *N=61* No further information	Patients recruited to a previous study on gastroscopic screening in pernicious anaemia. Population strata (previous gastric surgery): not reported Age: 20-79 years (median 63 years at first investigation) 35 women, 44 men	At mean 6.4 years: Mortality Gastric carcinoma	Unclear how 12 patients were selected for regular follow up Conducted in UK
Sjoblom 1988 [6]	**Gastroscopy** *N= 71* Gastroscopic screening	Patients with pernicious anaemia, examined as inpatients (1972-	At mean 7 years: Gastric carcinoid tumours	Criteria for diagnosis of PA: 1. Macrocytic anaemia and/or megaloblastic

Study	Intervention and comparison	Population	Outcomes	Comments
	Versus **No monitoring** *N=34* Patients who did not attend screening.	1985) or outpatients (1980-1985); aged ≤75 years Population strata (previous gastric surgery): no information reported Age: ≤75 years, no further information reported Sex: no information reported	Gastric carcinoma	bone marrow and/or subnormal serum levels of vitamin B12. 2. Schilling test showing intrinsic factor deficiency, pentagastrin-fast achlorhydria or histologically verified fundic atrophic gastritis. Conducted in Finland

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 4: Clinical evidence summary: Gastroscopy at 24 months versus gastroscopy at 48 months (RCT evidence)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with gastroscopy at 48 months	Risk difference with Gastroscopy at 24 months
Carcinoid tumours	42 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	**OR 0.12** (0.00 to 6.20)	50 per 1,000	**50 fewer per 1,000** (180 fewer to 80 more)[d]

a. High risk of bias due to lack of information reported on the randomisation process, deviations from the intended interventions and missing outcome data

b. Very serious population indirectness due to lack of information reported on previous gastric surgery and not all participants having pernicious anaemia

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

d. Absolute effects calculated using risk difference

Table 5: Clinical evidence summary: Gastroscopy (mean every 14 months) versus no monitoring

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no monitoring	Risk difference with Gastroscopy (mean every 14 months)
Mortality	73 (1 observational study)	⊕◯◯◯ Very low[a,b,c]	**RR 0.73** (0.10 to 5.38)	115 per 1,000	**31 fewer per 1,000** (103 fewer to 503 more)
Gastric carcinoma	73 (1 observational study)	⊕◯◯◯ Very low[b,d,e]	**RD 0.00** (-0.11 to 0.11)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. Very high risk of bias due to confounding and classification of interventions

b. Serious population indirectness due to lack of information reported on previous gastric surgery

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

d. Very high risk of bias due to confounding, classification of interventions and measurement of outcomes

e. Serious imprecision (risk difference and sample size >70<350)

Table 6: Clinical evidence summary: Gastroscopic screening versus no monitoring

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no monitoring	Risk difference with Gastroscopic screening
Carcinoid tumours	105 (1 observational study)	⊕◯◯◯ Very low[a,b,c]	**OR 4.66** (0.69 to 31.45)	0 per 1,000	**70 more per 1,000** (0 fewer to 140 more)[d]
Gastric carcinoma	105 (1 observational study)	⊕◯◯◯ Very low[a,b,e]	**RD 0.00** (-0.04 to 0.04)	0 per 1,000	**0 fewer per 1,000** (40 fewer to 40 more)

a. Very high risk of bias due to confounding, classification of interventions and missing data

b. Serious population indirectness due to lack of information reported on previous gastric surgery

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

d. Absolute effect calculated using risk difference

e. Serious imprecision (risk difference and sample size >70<350)

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study with relevant comparisons was included in this review.[3] The study compared using monitoring for cancer using gastroscopy in different population groups. This is summarised in the health economic evidence profile below (Table 7) and the health.

The patient population in the included study all had underlying atrophic gastritis, pernicious anaemia was a stratum in the study.

1.1.7.2 Excluded studies

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

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

1.1.8 Summary of included economic evidence

Table 7: Health economic evidence profile: Gastroscopy surveillance for people with pernicious anaemia

Study	Applicability	Limitations	Other comments	Incremental cost[(c)]	Incremental effects	Cost effectiveness	Uncertainty
Lahner 2017 [3](Italy)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Simple cost-effectiveness analysis based on cohort from Italy. • Population: Pernicious anaemia • A) without extensive atrophy (n=79) • B) with extensive atrophy (n=23) Time horizon: 7.5 years (range 4 – 23.4 years)	A) £376 B) £234	A) 2/79 B) 2/23	A) £13,346 per cancer detected B) £2,692 per cancer detected	No sensitivity analysis reported.

(a) The population included all have pernicious anaemia with an appropriate intervention – gastroscopy as per the protocol. Although the study does not have a UK NHS perspective, the study is conducted in a similar system compared to the NHS and the healthcare perspective used is appropriate. The use of gastroscopy also reflects current practice in the NHS. However, no QALYs reported. Furthermore, discounting is not applied/reported.

(b) QALYs are not reported, and health outcomes are not included. The only cost incorporated is gastroscopy, no other costs such as treatment costs are reported or the costs of further investigations such as biopsy. There was no sensitivity analysis conducted. The sample size was small.

(c) 2017 Italy Euros converted to UK pounds[5]. Cost components incorporated: Gastroscopy.

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1. The outcomes that matter most

The committee considered mortality, quality of life, diagnosis of cancer, stage of cancer at diagnosis or surgical resectability, incidence of gastric neuroendocrine tumours and procedure related adverse events including bleeding, perforation, and aspiration to be the most important outcomes of monitoring for gastric cancer. All outcomes were considered equally important for decision making and therefore were all rated as critical.

The purpose of the outcome of stage of cancer at diagnosis or surgical resectability was to determine whether the monitoring strategies help to identify cancer earlier, i.e., before it progresses to a higher stage, or beyond surgical removal. However, no evidence was identified for this outcome. No evidence was identified for quality of life, or procedure related adverse events.

1.1.9.2 The quality of the evidence

Evidence came from one randomised controlled trial comparing different lengths of gastroscopic follow up and two observational cohort studies comparing gastroscopic follow up with no monitoring. The quality of the evidence for all identified outcomes was very low. The main reasons for downgrading of the quality of the evidence were indirectness, risk of bias and imprecision. No evidence was identified for monitoring with barium meal, pepsinogen, gastrin, or any combination/staged protocols using pepsinogen and gastrin.

One of the main reasons for downgrading the quality of the evidence was population indirectness. The committee decided when setting the review protocol to stratify the evidence for people who have undergone previous gastric surgery, as the associated risk of developing gastric cancer is higher in this group. However, none of the included studies reported this information, therefore all outcomes were downgraded for serious population indirectness. In addition, the study population in the randomised controlled trial was people with body-predominant atrophic gastritis, 60 per cent of whom had pernicious anaemia. As 40 per cent of the study population did not have pernicious anaemia, the evidence from this study was downgraded further for population indirectness. The committee considered the evidence to be relevant to this review as people with pernicious anaemia have atrophic gastritis and it is the atrophic gastritis that increases the risk of gastric cancer rather than the pernicious anaemia itself.

The committee noted the age of the studies, particularly those conducted over 30 years ago. The committee considered that endoscopic techniques have greatly improved since the studies were carried out and more detailed imaging is now available, allowing detection of smaller or more subtle abnormalities. Therefore, the evidence identified may underestimate the effectiveness of gastroscopic monitoring.

All evidence was at high or very high risk of bias. In the randomised controlled trial, this was due to the lack of information reported on the randomisation process, deviations from the intended interventions and missing outcome data. In the observational studies, this was due to the lack of adjustment for confounders, classification of interventions and missing data.

The included studies all had small samples sizes, around 100 participants or less. This led to imprecision around several of the point estimates. The committee were aware that around one in 300 people with autoimmune gastritis per year develop gastric cancer. Therefore, the studies were likely to be underpowered to detect any meaningful differences between the monitoring strategies.

Considering all the limitations outlined above, the committee considered there to be insufficient evidence upon which to base recommendations. The committee agreed that this

is an area in which further research is needed and therefore decided to make a recommendation for research.

1.1.9.3 Benefits and harms

All the evidence identified was for gastroscopy, with no evidence identified for any other monitoring technique listed in the review protocol. The committee noted that gastroscopy is the only technique that can detect the presence of gastric cancer in people with symptoms. The other methods are more appropriate in the context of assessing risk of developing cancer in people who are asymptomatic.

Very low-quality evidence suggested a benefit of regular gastroscopy over no monitoring for reducing mortality, although there was very serious imprecision, with wide confidence intervals compatible with no difference and a harm of gastroscopy. Very low-quality evidence also showed a benefit of gastroscopic screening over no monitoring for increasing the identification of carcinoid tumours. No clinically important difference was found between 24 and 48 month follow up with gastroscopy in the identification of carcinoid tumours. No clinically important difference was found between regular gastroscopy or gastroscopic screening compared with no monitoring for gastric carcinoma. The committee considered there to be insufficient evidence upon which to base recommendations.

The committee considered what is being done in current clinical practice. Gastroscopy on diagnosis of autoimmune gastritis is not carried out routinely and referral to secondary care depends on local interest and locally available services, GP knowledge and awareness, and tradition. The committee also considered the potential harms of gastroscopic screening or monitoring. No evidence was identified for quality of life or procedure related adverse events; however, the committee discussed the physically uncomfortable nature of the procedure from the patients' perspective. Therefore, the committee agreed that without sufficient evidence to recommend gastroscopic surveillance for gastric cancer in all people with autoimmune gastritis, gastroscopy should only be offered if there is a clinical reason for doing so.

If there are symptoms of gastric cancer present, such as new dysphagia, or dyspepsia, nausea and vomiting and weight loss in over 55's, people are referred urgently to gastroenterology through the two-week cancer referral pathway. Biopsies are taken at gastroscopy and only those with high operative link for gastritis assessment (OLGA) and operative link for gastric intestinal metaplasia assessment (OLGIM) scores would have subsequent or regular gastroscopic monitoring. Identification of small tumours (<10mm) for example, require surveillance rather than treatment. The committee recommended that healthcare professionals consider referral for gastroscopic endoscopy if the person has autoimmune gastritis with new onset upper gastrointestinal symptoms.

The committee highlighted the need for greater awareness on the upper gastrointestinal symptoms, as well as the increased risk of gastric adenocarcinoma and gastric neuroendocrine tumours in people with autoimmune gastritis. Therefore, this information was included in the wording of the recommendations in the hope that this will raise awareness, particularly among GPs. The committee were also aware of the NICE guideline on Suspected cancer and cross referred to the recommendations on lower and upper gastrointestinal tract cancers.

1.1.9.4 Cost effectiveness and resource use

Economic evidence

One economic evaluation was identified for this review. The economic evaluation investigated the cost to detect cancer for people with autoimmune gastritis compared to people with additional risk factors with autoimmune gastritis using gastroscopy surveillance. The patient population in the included study all had underlying atrophic gastritis, autoimmune

gastritis was a stratum in the study. The committee considered only the results for people with autoimmune gastritis.

In the economic evaluation, the cost to detect a cancer for an autoimmune gastritis patient without extensive atrophic gastritis was £14,486 whilst the cost to detect a cancer in an autoimmune gastritis patient population with extensive atrophic gastritis was £2,692.

The only reported cost was the cost of the gastroscopy (endoscopy) which was valued at £155. There were no costs of cancer treatment included. Routine gastroscopy was not recommended due to the limitations of the study which didn't consider quality-adjusted life-years or the cost of cancer treatment. Also, the reported gastroscopy cost was deemed to be significantly lower than other published costs; there is a cost of £754 reported in the 'National schedule of NHS costs 2020-2021' which would raise the cost to detect gastric cancer to approximately £70,000 for people without extensive atrophic gastritis. This would then potentially have a significant resource impact on the NHS. Furthermore, there was a relatively small sample of people with autoimmune gastritis (102 people) which added to the uncertainty of the results. This was also a non-UK based study which raised applicability concerns.

No cost-effectiveness evidence was identified for other interventions for monitoring of gastric cancer in people with autoimmune gastritis. There was no evidence for the use of barium meal, pepsinogen, gastrin, or any combination/staged protocols using pepsinogen and gastrin for monitoring.

Potential for modelling

The committee considered whether it would be feasible to model the cost-effectiveness of gastroscopy for surveillance of gastric cancer for people with autoimmune gastritis. The committee thought that earlier treatment could lead to better outcomes and care savings but there is not the evidence to quantify these outcomes.

The committee noted that gastroscopy was not always preferred by people due to the uncomfortable nature of the intervention which may impact their utility whilst undergoing the screening. From the clinical review, there was no evidence relating to quality of life.

The committee were concerned about the lack of available clinical data to inform an economic model specifically for people with autoimmune gastritis and the outcomes for people with autoimmune gastritis that are diagnosed with gastric cancer. The committee were unaware of data relating to the incidence of gastric cancer in people with autoimmune gastritis and the type of cancer as well as stage of cancer when detected. The committee considered whether evidence from other clinical conditions could inform modelling, but they were concerned about the clinical validity of extrapolating evidence from other clinical conditions.

Conclusions about cost effectiveness

There is a substantial cost of offering gastroscopic surveillance of £754 every 2-4 years. Earlier identification may improve treatment outcomes and patient QALYs however there is too much uncertainty and lack of evidence to indicate whether the cost-effectiveness of providing routine gastroscopy is less than £20,000 per QALY gained.

There was no evidence at all for other forms of surveillance.

Recommendations

Due to insufficient clinical and cost effectiveness evidence, recommendations for gastroscopy to be offered routinely for surveillance could not be made. There was no evidence at all for other forms of surveillance. The committee members decided to recommend investigating what monitoring should be offered to people with autoimmune

gastritis to identify gastric cancer as a research question, and this topic was not subsequently modelled.

The committee also recommended that clinicians look out for symptoms that might suggest cancer and cross-referred to relevant NICE guidance on cancer diagnosis.

Resource impact

The committee members think that some people with autoimmune gastritis that have gastrointestinal symptoms may already be receiving gastroscopic surveillance. Although there was not enough evidence to recommend routine surveillance, the committee did not expect surveillance to stop and so it is not thought there will be any additional resource impact.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1 and 1.7.2, and the research recommendation on what monitoring should be offered to people with autoimmune gastritis (also known as pernicious anaemia) to identify gastric cancer.

1.1.11 References

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6. Sjoblom SM, Sipponen P, Miettinen M, Karonen SL, Jrvinen HJ. Gastroscopic screening for gastric carcinoids and carcinoma in pernicious anemia. Endoscopy. 1988; 20(2):52-56

Appendices

Appendix A – Review protocols

Review protocol for monitoring for gastric cancer in people with pernicious anaemia

ID	Field	Content
0.	PROSPERO registration number	CRD42022345215
1.	Review title	What monitoring should be offered to people with pernicious anaemia to identify gastric cancer?
2.	Review question	What monitoring should be offered to people with pernicious anaemia to identify gastric cancer?
3.	Objective	To identify the most clinically and cost-effective monitoring strategy to identify gastric cancer in people with pernicious anaemia, including the type of procedures and frequency.
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 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	Pernicious anaemia
6.	Population	Inclusion: adults with diagnosed pernicious anaemia (diagnosis as defined by the studies) Exclusion: other types/causes of vitamin B12 deficiency Strata: • Other risk factors for gastric cancer (patients with any previous gastric surgery, including bariatric surgery)
7.	Intervention	• Monitoring for gastric cancer: ○ Gastroscopy ○ Barium meal ○ Pepsinogen (followed by gastroscopy for those at high risk) ○ Gastrin (followed by gastroscopy for those at high risk) ○ Combined pepsinogen + gastrin (followed by gastroscopy for those at high risk) ○ 3 staged pepsinogen, followed by gastrin (followed by gastroscopy for those at high risk) ○ 3 staged gastrin, followed by pepsinogen (followed by gastroscopy for those at high risk) Stratify by: • Frequency
8.	Comparator	• All monitoring strategies compared with each other (what is included and frequency of monitoring) • No monitoring
9.	Types of study to be included	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered)

		Key confounders: previous gastric surgery 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	NA

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
		
		• Mortality
		• Quality of life
		• Diagnosis of cancer
		• Stage of cancer at diagnosis/surgical resectability
		• Incidence of gastric neuroendocrine tumours (AKA carcinoid tumours/NETS/NENS)
		• Adverse events (procedure related):
		  ○ bleeding
		  ○ perforation
		  ○ aspiration

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 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.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Randomised Controlled Trial: Cochrane RoB (2.0) Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Non randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness,

		inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.		
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Age (older adults >65 years and younger adults <65 years) • Sex (study defined)		
17.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	27/07/2022		
21.	Anticipated completion date	01/11/2023		
22.		Review stage	Started	Completed

	Stage of review at time of this submission	Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer] Toby Sands [Systematic reviewer]		

		Aamer Jawed [Health economist] Stephen Deed [Information specialist] Katie Tuddenham [Project manager]
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE
28.	Other registration details	
29.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022345215
30.	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.
31.	Keywords	

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

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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 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. 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).[4] **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 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 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[4]

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

B.1 What monitoring should be offered to people with pernicious anaemia to identify gastric cancer?

B.1.1 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. No search filters were applied.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 13 December 2022	Exclusions (animal studies, letters, comments, editorials,

Database	Dates searched	Search filter used
		case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, 13 December 2022 Cochrane Central Register of Controlled Trials to Issue 12 of 12, 13 December 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 13 December 2022	Systematic review Exclusions (Cochrane reviews)

1 **Medline (Ovid) search terms**

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25

27.	limit 26 to English language
28.	Gastrointestinal Neoplasms/ or Stomach Neoplasms/ or Neuroendocrine Tumors/
29.	((gastric or stomach or gastrointestin* or gastroesophag* or gastro esophag* or gastrooesophag* or gastro oesophag* or neuroendocrin* or neuro endocrin*) adj3 (cancer* or carcinoma* or carcinogenesis or carcinoid or adenocarcinom* or leiomyosarcoma* or lymphoma* or tumour* or tumor* or neoplas* or malignan* or metaplas* or metast* or dysplasi*)).ti,ab,kf.
30.	28 or 29
31.	27 and 30

1 **Embase (Ovid) search terms**

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	exp gastrointestinal tumor/ or exp stomach tumor/ or neuroendocrine tumor/ or neuroendocrine carcinoma/
28.	((gastric or stomach or gastrointestin* or gastroesophag* or gastro esophag* or gastrooesophag* or gastro oesophag* or neuroendocrin* or neuro endocrin*) adj3 (cancer* or carcinoma* or carcinogenesis or carcinoid or adenocarcinom* or leiomyosarcoma* or lymphoma* or tumour* or tumor* or neoplas* or malignan* or metaplas* or metast* or dysplasi*)).ti,ab,kf.
29.	27 or 28
30.	26 and 29

1

2 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Vitamin B 12 Deficiency] explode all trees
#2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) near/4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)):ti,ab
#3.	MeSH descriptor: [Anemia, Macrocytic] explode all trees
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) near/3 (anemia* or anaemia*)):ti,ab
#5.	MeSH descriptor: [Intrinsic Factor] this term only
#6.	intrinsic factor:ti,ab
#7.	(or #1-#6)
#8.	conference:pt or (clinicaltrials or trialsearch):so
#9.	#7 not #8
#10.	MeSH descriptor: [Gastrointestinal Neoplasms] this term only
#11.	MeSH descriptor: [Stomach Neoplasms] this term only
#12.	MeSH descriptor: [Neuroendocrine Tumors] this term only
#13.	((gastric or stomach or gastrointestin* or gastroesophag* or gastro esophag* or gastrooesophag* or gastro oesophag* or neuroendocrin* or neuro endocrin*) NEAR/3 (cancer* or carcinoma* or carcinogenesis or carcinoid or adenocarcinom* or leiomyosarcoma* or lymphoma* or tumour* or tumor* or neoplas* or malignan* or metaplas* or metast* or dysplasi*)):ti,ab,kW
#14.	(or #10-#13)
#15.	#9 and #14

3 **Epistemonikos search terms**

1.	(title:("b12 deficien*" OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor") OR abstract:("b12 deficien*" OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor")) AND (title:("gastric malignan*" OR "gastric metaplas*" OR "gastric metast*" OR "gastric dysplasi*" OR "stomach malignan*" OR "stomach metaplas*" OR "stomach metast*" OR "stomach dysplasi*" OR "gastric cancer*" OR "gastric adenocarcinom*" OR "gastric carcinom*" OR "gastric tumour*" OR "gastric tumor*" OR "gastric neoplas*" OR "stomach cancer*" OR "stomach adenocarcinom*" OR "stomach carcinom*" OR "stomach tumour*" OR "stomach tumor*" OR "stomach neoplas*" OR "gastrointestin* cancer*" OR "gastrointestin* adenocarcinom*" OR "gastrointestin* carcinom*" OR "gastrointestin* tumour*" OR "gastrointestin* tumor*" OR "gastrointestin* neoplas*") OR abstract:("gastric malignan*" OR "gastric metaplas*" OR "gastric metast*" OR "gastric dysplasi*" OR "stomach malignan*" OR "stomach metaplas*" OR "stomach metast*" OR "stomach dysplasi*" OR "gastric cancer*" OR "gastric adenocarcinom*" OR "gastric carcinom*" OR "gastric tumour*" OR "gastric tumor*" OR "gastric neoplas*" OR "stomach cancer*" OR "stomach adenocarcinom*" OR "stomach carcinom*" OR "stomach tumour*" OR "stomach tumor*" OR "stomach

	neoplas*" OR "gastrointestin* cancer*" OR "gastrointestin* adenocarcinom*" OR "gastrointestin* carcinom*" OR "gastrointestin* tumour*" OR "gastrointestin* tumor*" OR "gastrointestin* neoplas*")

B.1.21 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Vitamin B12 deficient 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 9: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2022	Health economics studies Quality of life studies
	Quality of Life 1946 – 16 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2022	Health economics studies Quality of life studies
	Quality of Life 1974 – 16 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31 March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31 March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2022	English language

Medline (Ovid) search terms

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.

3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	quality-adjusted life years/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/28-46
48.	Economics/
49.	Value of life/
50.	exp "Costs and Cost Analysis"/
51.	exp Economics, Hospital/
52.	exp Economics, Medical/
53.	Economics, Nursing/
54.	Economics, Pharmaceutical/
55.	exp "Fees and Charges"/
56.	exp Budgets/
57.	budget*.ti,ab.
58.	cost*.ti.
59.	(economic* or pharmaco?economic*).ti.
60.	(price* or pricing*).ti,ab.
61.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
62.	(financ* or fee or fees).ti,ab.
63.	(value adj2 (money or monetary)).ti,ab.
64.	or/48-63
65.	27 and 47
66.	27 and 64
67.	limit 66 to yr="2014 -Current"
68.	65 or 67

1 **Embase (Ovid) search terms**

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract or conference paper).pt.

14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	quality adjusted life year/
28.	"quality of life index"/
29.	short form 12/ or short form 20/ or short form 36/ or short form 8/
30.	sickness impact profile/
31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
48.	or/27-47
49.	health economics/
50.	exp economic evaluation/
51.	exp health care cost/
52.	exp fee/
53.	budget/
54.	funding/
55.	budget*.ti,ab.
56.	cost*.ti.
57.	(economic* or pharmaco?economic*).ti.
58.	(price* or pricing*).ti,ab.

59.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
60.	(financ* or fee or fees).ti,ab.
61.	(value adj2 (money or monetary)).ti,ab.
62.	or/49-61
63.	26 and 48
64.	26 and 62
65.	limit 64 to yr="2014 -Current"
66.	63 or 65

NHS EED and HTA (CRD) search terms

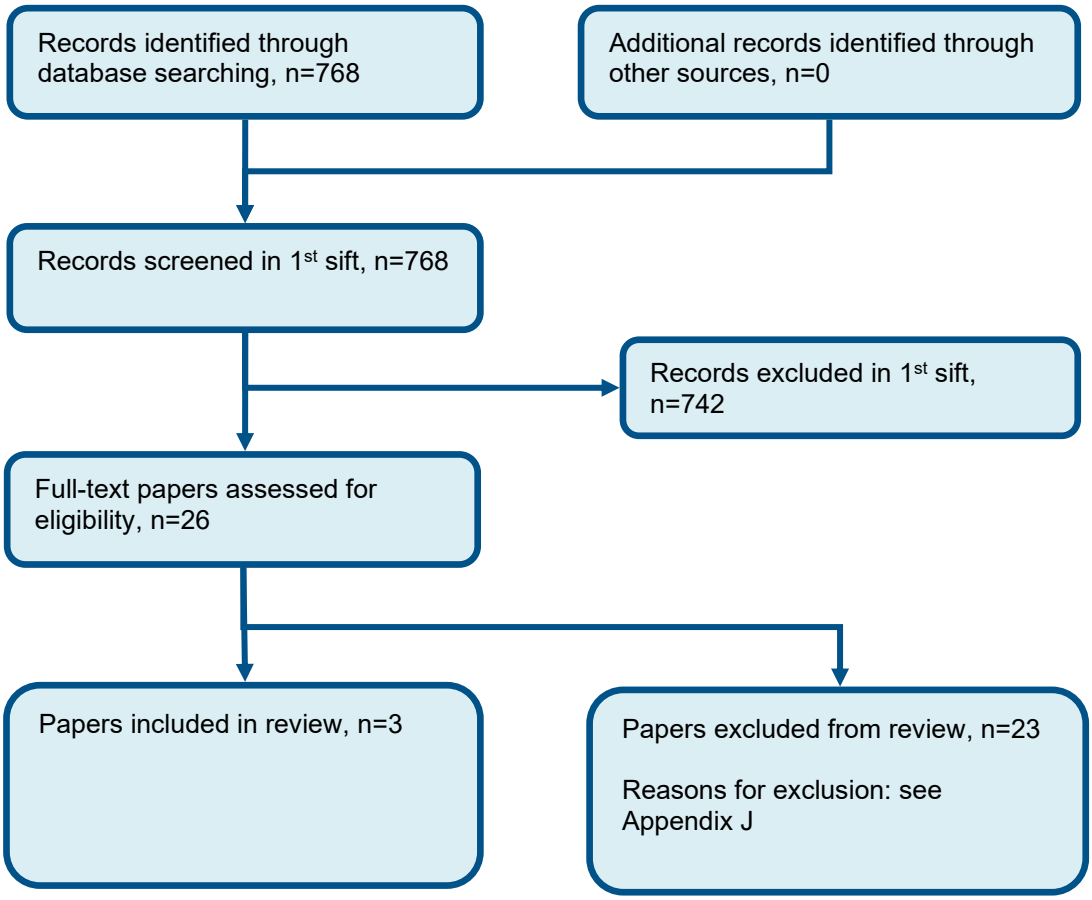
#1.	MeSH DESCRIPTOR Vitamin B 12 Deficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Anemia, Macrocytic EXPLODE ALL TREES
#3.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis))
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*))
#5.	(intrinsic factor)
#6.	#1 OR #2 OR #3 OR #4 OR #5

INAHTA search terms

1.	(Anemia, Pernicious)[mh] OR (Vitamin B 12 Deficiency)[mh] OR (pernicious anemia) OR (pernicious anemia) OR (B12) OR (B 12)

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of monitoring for gastric cancer in people with pernicious anaemia



Appendix D – Effectiveness evidence

Armbrecht, 1990

Bibliographic Reference	Armbrecht, U; Stockbrugger, R W; Rode, J; Menon, G G; Cotton, P B; Development of gastric dysplasia in pernicious anaemia: a clinical and endoscopic follow up study of 80 patients.; Gut; 1990; vol. 31 (no. 10); 1105-9

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	UK
Study setting	Hospital and patients' homes.
Study dates	1978-1980 - initial recruitment 1980-1985 - regular monitoring of 12 patients 1985-1986 - follow up
Sources of funding	Not reported.

Inclusion criteria	Proved pernicious anaemia.
Exclusion criteria	Total gastrectomy.
Recruitment / selection of participants	Follow up study in patients recruited to a previous study on gastroscopic screening in pernicious anaemia.
Intervention(s)	Histories of clinical symptoms taken and upper gastrointestinal endoscopies performed at a mean interval of 14 months. At every endoscopy, at least three biopsy specimens each were obtained from the gastric mid-body, the prepyloric antrum, the second part of the duodenum, and from all visible lesions. In addition, biopsy specimens were taken for electron microscopy and for immunohistological studies.
Population subgroups	Population strata (previous bariatric surgery): not reported Population subgroups (age): 20 to 79 years (median 63 years at the first investigation) Population subgroups (sex): 35 women, 44 men
Comparator	No monitoring (no further details).
Number of participants	79
Duration of follow-up	mean 6.4 years
Indirectness	Population indirectness: serious due to lack of information on previous gastric surgery.
Additional comments	NA

Study arms

Gastroscopy (N = 12)

Histories of clinical symptoms were taken and upper gastrointestinal endoscopies were performed at a mean interval of 14 months. At every endoscopy, at least three biopsy specimens each were obtained from the gastric mid-body, the prepyloric antrum, the second part of the duodenum, and from all visible lesions. In addition, biopsy specimens were taken for electron microscopy and for immunohistological studies.

No monitoring (N = 61)
No further information

Characteristics

Study-level characteristics

Characteristic	Study (N = 79)
% Female Nominal	35
Mean age (SD) Range	20 to 79
Mean age (SD) Custom value	median 63 years

Outcomes

Study timepoints

- 6.4 year (mean 6.4 years (6-7 years from initial screening))

Gastroscopy versus no monitoring

Outcome	Gastroscopy, 6.4 year, N = 12	No monitoring, 6.4 year, N = 61
Mortality Nominal	1	7
Gastric carcinoma	0	0

Outcome	Gastroscopy, 6.4 year, N = 12	No monitoring, 6.4 year, N = 61
Nominal		

Critical appraisal - ROBINS-I checklist
Gastroscopy versus no monitoring-Mortality-Nominal-Gastroscopy-No monitoring-t6.4

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable

Critical appraisal - ROBINS-I checklist
Gastroscopy versus no monitoring-Gastric carcinoma-Nominal-Gastroscopy-No monitoring-t6.4

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable

Lahner, 2001

Bibliographic Reference	Lahner, E; Caruana, P; D'Ambra, G; Ferraro, G; Di Giulio, E; Delle Fave, G; Bordi, C; Annibale, B; First endoscopic-histologic follow-up in patients with body-predominant atrophic gastritis: when should it be done?.; Gastrointestinal endoscopy; 2001; vol. 53 (no. 4); 443-8

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	Italy
Study setting	Outpatients
Study dates	not reported
Sources of funding	Supported by a grant from the Italian Ministry for the University, n.02/12/01/10 1995-98 and by a grant by FIMAD
Inclusion criteria	Outpatients with BAG were recruited in a screening program for early detection of BAG in patients with unexplained anaemia or long-standing dyspepsia. Criteria for diagnosis of body–predominant atrophic gastritis: fasting gastrin above upper normal values, hypochlorhydria/achlorhydria to pentagastrin stimulation, and histologic confirmation of gastric body mucosal atrophy.

	Criteria for diagnosis of pernicious anaemia: macrocytic anaemia (haemoglobin levels less than 14 g/dL for men and less than 12 g/dL for women; mean corpuscular volume greater than 100 fL), vitamin B12 levels less than 220 pg/mL (normal range 220 to 1130 pg/mL), recovery from anaemia after treatment with intramuscular vitamin B12, hypochlorhydria/achlorhydria to pentagastrin stimulation, and histologic confirmation of gastric body mucosa atrophy.
Exclusion criteria	Patients with neoplastic and preneoplastic lesions at the time of diagnosis of BAG as well as patients treated to eradicate Helicobacter pylori.
Recruitment / selection of participants	Consecutive, recruited in a screening program for early detection of BAG in patients with unexplained anaemia or long-standing dyspepsia.
Intervention(s)	EGD with biopsies taken in the gastric antrum and body (3 from each site) for conventional histopathologic examination and for the evaluation of endocrine cells. Serologic tests for fasting gastrin and pepsinogen I were also obtained.
Population subgroups	Population strata (previous gastric surgery): not reported Population subgroups (age): mixed Population subgroups (sex): mixed
Comparator	24 versus 48 months
Number of participants	61
Duration of follow-up	range 20 - 60 months
Indirectness	Population indirectness: very serious due to not all participants having pernicious anaemia and lack of reporting on previous gastric surgery.

Study arms

Gastroscopy at 24 months (N = 30)

Invited to undergo follow-up at a median of 24 months (range 20 to 26 months) after diagnosis of body-predominant atrophic gastritis.

Gastroscopy at 48 months (N = 31)

Follow-up scheduled at a median of 48 months (range 38 to 60 months).

Characteristics

Study-level characteristics

Characteristic	Study (N = 61)
% Female Custom value	M:F 15:27
Mean age (SD) Custom value	median (range): 57 (22-73 years)
Pernicious anaemia (number of participants with pernicious anaemia) Patients with pernicious anaemia were significantly older than those without. There were no significant differences with respect to other clinical features. With regard to baseline and follow-up patterns of atrophy and intestinal metaplasia as well as fasting gastrin and pepsinogen I levels, no significant differences between patients with and without pernicious anaemia were found. Custom value	59.5%

Arm-level characteristics

Characteristic	Gastroscopy at 24 months (N = 30)	Gastroscopy at 48 months (N = 31)
H. pylori status (number of participants with positive H. pylori status) Nominal	4	4

Outcomes

Study timepoints

- Baseline
- 4 year (Follow up (2 versus 4 years))

Gastroscopy at 24 months versus gastroscopy at 48 months

Outcome	Gastroscopy at 24 months, Baseline, N = 22	Gastroscopy at 24 months, 4 year, N = 22	Gastroscopy at 48 months, Baseline, N = 20	Gastroscopy at 48 months, 4 year, N = 20
Carcinoid tumours (Number of people with carcinoid tumours) One participant with PA in the 4 year follow up group had a carcinoid tumour at follow up endoscopy. The tumour was removed endoscopically. Nominal	0	0	0	1

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

Gastroscopyat24monthsversusgastroscopyat48months-Carcinoidtumours-Nominal-Gastroscopy at 24 months-Gastroscopy at 48 months-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Sjoblom, 1988

Bibliographic Reference	Sjoblom, S M; Sipponen, P; Miettinen, M; Karonen, S L; Jrvinen, H J; Gastroscopic screening for gastric carcinoids and carcinoma in pernicious anemia.; Endoscopy; 1988; vol. 20 (no. 2); 52-6

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	Finland
Study setting	Single hospital
Study dates	1972-1985
Sources of funding	Not reported
Inclusion criteria	Patients with pernicious anaemia, examined as inpatients (1972-1985) or outpatients (1980-1985); aged ≤75 years Criteria for diagnosis of PA: 1. Macrocytic anaemia and/or megaloblastic bone marrow and/or subnormal serum levels of vitamin B12.

	2. Schilling test showing intrinsic factor deficiency, pentagastrin-fast achlorhydria or histologically verified fundic atrophic gastritis.
Exclusion criteria	Death or gastrectomy before invitation for screening.
Recruitment / selection of participants	Those examined as inpatients (1972-1985) or outpatients (1980-1985) at a single hospital, no further details.
Intervention(s)	Gastroduodenoscopies with multiple antral and fundic mucosal biopsies performed by one endoscopist. All local changes such as discoloured spots or polypoid lesions were biopsied separately. Specimens were examined and classified by the same pathologist. State of antral and fundic mucosa was classified as normal, superficial chronic gastritis, mild, moderate or severe atrophic gastritis. Carcinoid tumours characterised in accordance with the classification of Soga and Tazawa. Blood drawn from fasting patients to determine serum gastrin, pepsinogen and neuron-specific enolase.
Population subgroups	Population strata (previous gastric surgery): no information reported. Population subgroups (age): ≤75 years, no further information reported Population subgroups (sex): no information reported
Comparator	Patients who did not attend screening, no further details. Information on possible gastric malignancies gathered from hospital records, the Finnish Cancer Registry and the Finnish Center of Statistics.
Number of participants	105
Duration of follow-up	0-20 years (mean 7 years)
Indirectness	Population indirectness: serious due to lack of information reported regarding previous gastric surgery.
Additional comments	None.

Study arms

Gastroscopy (N = 71)

Study location	Cohort study

Gastroscopic screening

No monitoring (N = 34)
Patients who did not attend screening.

Outcomes

Study timepoints

- 7 year (mean 7 years (range 0-20))

Gastroscopic screening versus no monitoring

Outcome	Gastroscopy, 7 year, N = 71	No monitoring, 7 year, N = 34
Gastric carcinoid tumours (Number of people with carcinoid tumours) Nominal	5	0
Gastric carcinoma (Number of people with gastric carcinoma) Nominal	0	0

Critical appraisal - ROBINS-I checklist

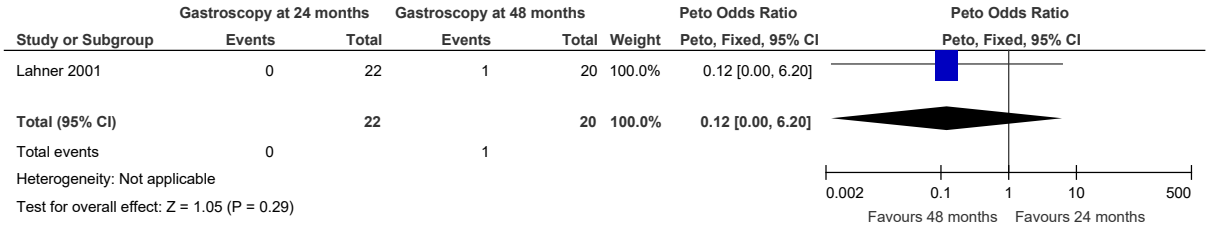
Gastroscopicscreeningversusnomonitoring-Gastriccarcinoidtumours-Nominal-Gastroscopy-No monitoring-t7

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Indirectly Applicable

Appendix E – Forest plots

E.1 Gastroscopy at 24 months versus gastroscopy at 48 months (RCT evidence)

Figure 2: Carcinoid tumours



E.2 Gastroscopy (mean every 14 months) versus no monitoring

Figure 3: Mortality at mean 6.4 years

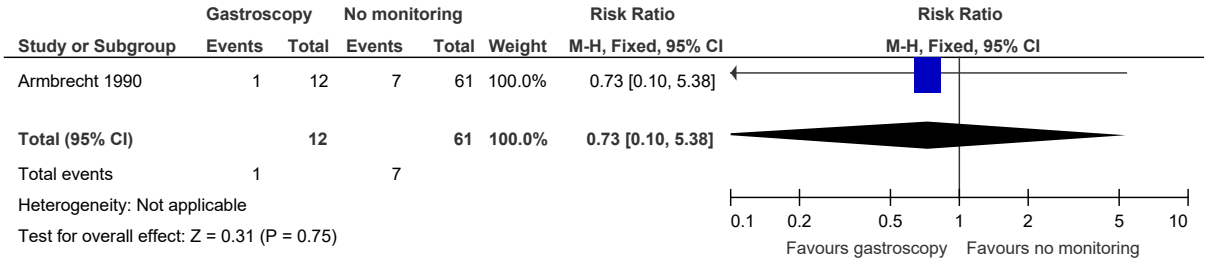


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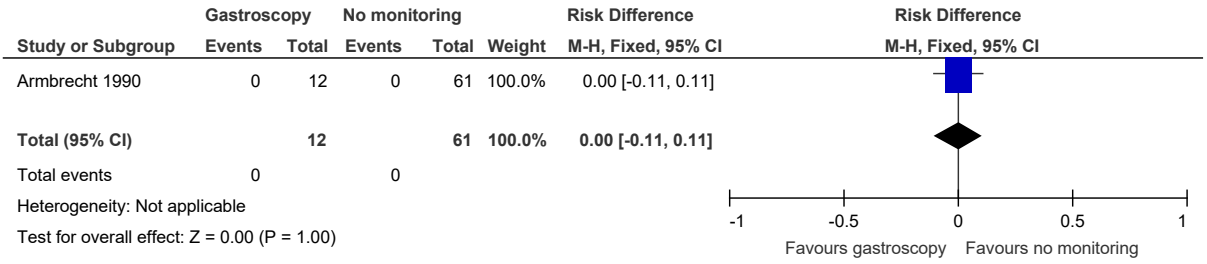
Figure 4: Gastric carcinoma at mean 6.4 years



E.3 Gastroscopic screening versus no monitoring

Figure 5: Carcinoid tumours at mean 7 years

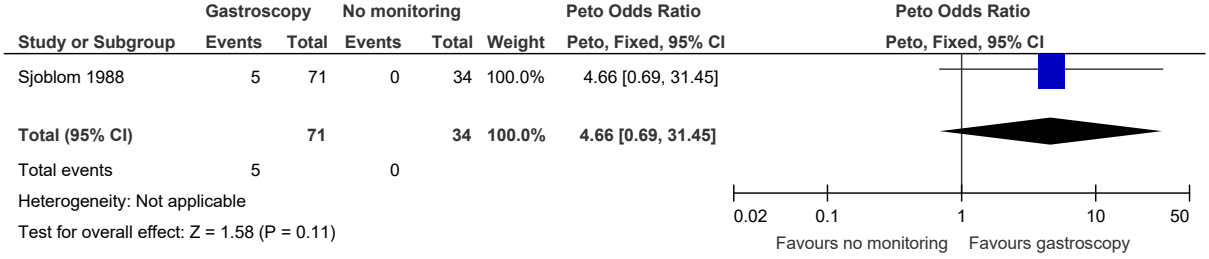


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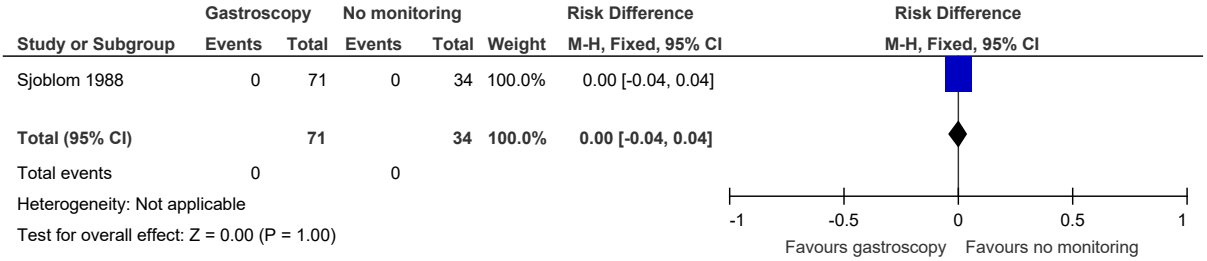
Figure 6: Gastric carcinoma at mean 7 years



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Appendix F – GRADE tables

Table 10: Clinical evidence profile: Gastroscopy at 24 months versus gastroscopy at 48 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gastroscopy at 24 months	gastroscopy at 48 months	Relative (95% CI)	Absolute (95% CI)		
Carcinoid tumours												
1	randomised trials	very serious[a]	not serious	very serious[b]	very serious[c]	none	0/22 (0.0%)	1/20 (5.0%)	**OR 0.12** (0.00 to 6.20)	**50 fewer per 1,000** (from 180 fewer to 80 more)[d]	⨁◯◯◯ Very low	CRITICAL

a. High risk of bias due to lack of information reported on the randomisation process, deviations from the intended interventions and missing outcome data

b. Very serious population indirectness due to lack of information reported on previous gastric surgery and not all participants having pernicious anaemia

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

d. Absolute effect calculated using risk difference

Table 11: Clinical evidence profile: Gastroscopy (mean every 14 months) versus no monitoring

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gastroscopy (mean every 14 months)	no monitoring	Relative (95% CI)	Absolute (95% CI)		
Mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gastroscopy (mean every 14 months)	no monitoring	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	very serious[a]	not serious	serious[b]	very serious[c]	none	1/12 (8.3%)	7/61 (11.5%)	**RR 0.73** (0.10 to 5.38)	**31 fewer per 1,000** (from 103 fewer to 503 more)	⨁◯◯◯ Very low	CRITICAL
Gastric carcinoma												
1	observational studies	very serious[d]	not serious	serious[b]	serious[e]	none	0/12 (0.0%)	0/61 (0.0%)	**RD 0.00** (-0.11 to 0.11)	**0 fewer per 1,000** (from 110 fewer to 110 more)	⨁◯◯◯ Very low	CRITICAL

a. Very high risk of bias due to confounding and classification of interventions

b. Serious population indirectness due to lack of information reported on previous gastric surgery

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

d. Very high risk of bias due to confounding, classification of interventions and measurement of outcomes

e. Serious imprecision (risk difference and sample size >70<350)

Table 12: Clinical evidence profile: Gastroscopic screening versus no monitoring

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gastroscopic screening	no monitoring	Relative (95% CI)	Absolute (95% CI)		
Carcinoid tumours												
1	observational studies	very serious[a]	not serious	serious[b]	very serious[c]	none	5/71 (7.0%)	0/34 (0.0%)	**OR 4.66** (0.69 to 31.45)	**70 more per 1,000** (from 0 fewer to 140 more)[d]	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gastroscopic screening	no monitoring	Relative (95% CI)	Absolute (95% CI)		
Gastric carcinoma												
1	observational studies	very serious[a]	not serious	serious[b]	serious[e]	none	0/71 (0.0%)	0/34 (0.0%)	**RD 0.00** (-0.04 to 0.04)	**0 fewer per 1,000** (from 40 fewer to 40 more)	⨁◯◯◯ Very low	CRITICAL

a. Very high risk of bias due to confounding, classification of interventions and missing data

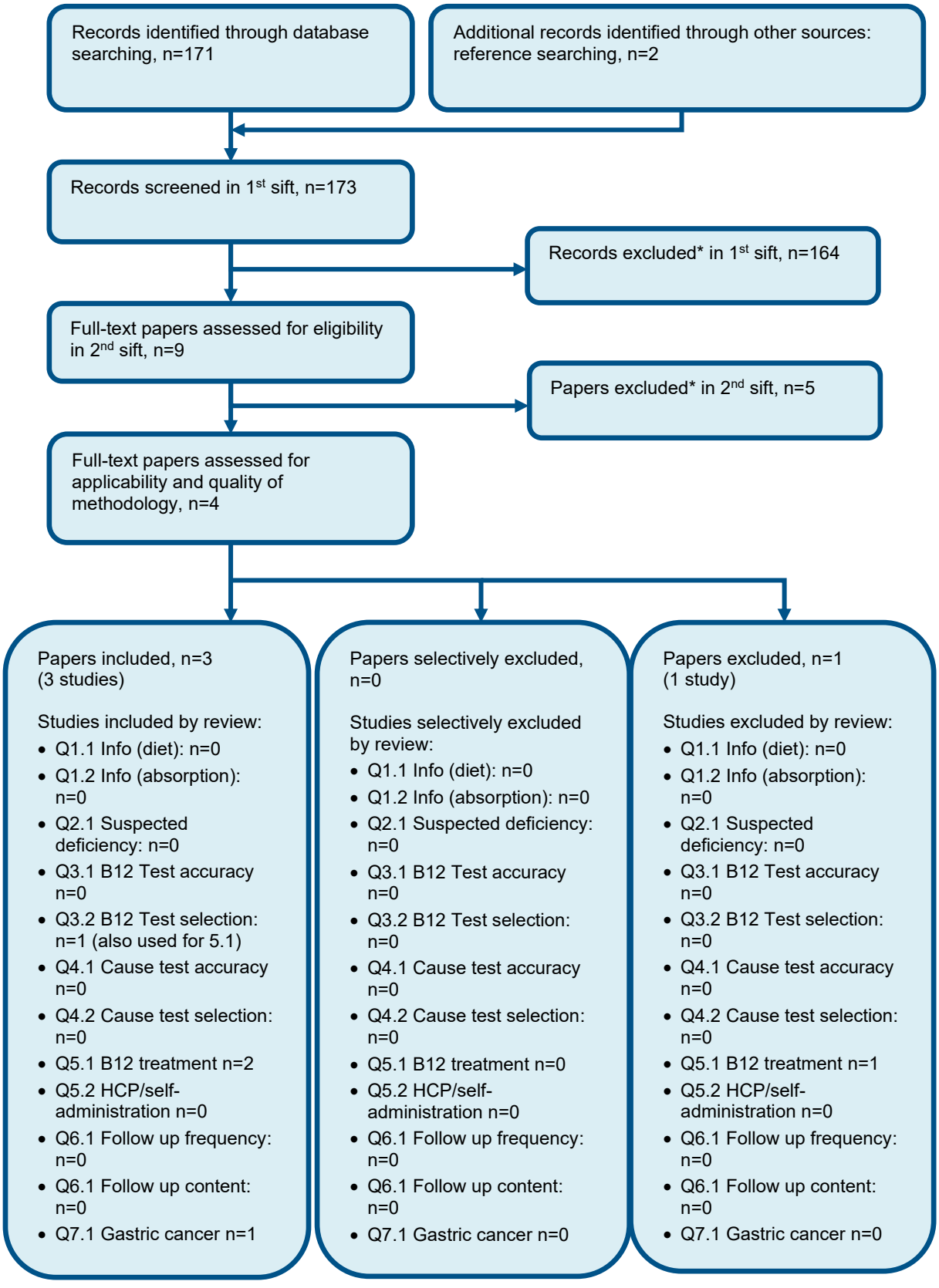
b. Serious population indirectness due to lack of information reported on previous gastric surgery

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

d. Absolute effect calculated using risk difference

e. Serious imprecision (risk difference and sample size >70<350)

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Lahner 2017[3]			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-effectiveness analysis (cancers detected) **Study design:** Cohort study **Approach to analysis:** Non simulated model based on real world data. **Perspective:** Italy NHS **Follow-Up: 7.5 years (**range 4 -23.4 years). **Discounting:** N/R	**Population:** People with pernicious anaemia **Cohort settings:** Age range 22-84 Male: 33% Interventions (surveillance strategies) in different groups which correspond to risk factors. **Intervention 1:** PA (n=102) **Intervention 2:** PA and extensive atrophy (n=23) **Intervention 3:** PA and OLGA 3-4 (n=18) **Intervention 4:** PA, age over 50 years and OLGA 3-4 (n=16) **Intervention 5:** PA and OLGIM 3-4 (n=8)	**Total costs:** Intervention 1: £29,692 Intervention 2: £5,385 Intervention 3: £4,154 Intervention 4: £3,692 Intervention 5: £1,538 **Currency & cost year:** 2017 Italy Euros (presented here as 2017 UK pounds[(b)]) **Cost components incorporated:** Gastroscopy	**Cancers detected:** Intervention 1:4/102 Intervention 2: 2/23 Intervention 3: 2/18 Intervention 4: 2/16 Intervention 5: 1/8	**Cost per cancer detected.** Intervention 1: £7,423 Intervention 2: £2,692 Intervention 3: £2,077 Intervention 4: £1,846 Intervention 5: £1,538 PA without extensive atrophy Intervention 1 vs 2 = £14,846 PA not OLGIM 3-4 Intervention 2 vs 5 = £ 3,846 **Analysis of uncertainty:** Sensitivity analysis was not conducted.
Data sources				
Health outcomes: Cancers detected, and number of gastroscopies were from an original cohort study. **Quality-of-life weights:** N/A. **Cost sources:** This unit cost of a gastroscopy was from the Italian society of Digestive Endoscopy.				

Comments
Source of funding: Grants from Sapienza University. **Limitations:** Not from a UK perspective. No QALYs or other health outcomes were reported. Furthermore, discounting is not applied/reported. The only cost incorporated is gastroscopy, no other costs such as cancer treatment are reported. Sensitivity analysis was not conducted. The sample size was small (and very small for some of the subgroups). Other: The full analysis included people with atrophic gastritis but not pernicious anaemia. Only the results for people for pernicious anaemia have been reported in this table.
Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: ICER= incremental cost-effectiveness ratio; NR= not reported OLGA = operative link of gastritis; OLGIM = operative link of intestinal; PA = pernicious anaemia.

(a) Converted using 2017 purchasing power parities[5]

(b) Directly applicable / Partially applicable / Not applicable

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

Appendix I – Health economic model

None.

Appendix J – Excluded studies

Clinical studies

Table 13: Studies excluded from the clinical review

Study	Code [Reason]
Affronti, J and Baillie, J (1994) Gastroscopic follow-up of pernicious anemia patients. Gastrointestinal endoscopy 40(1): 129	- Review article but not a systematic review
Anonymous. (1998) The role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal tract. Gastrointestinal Endoscopy 48(6): 663-668	- Guideline
Arvanitakis, C.; Holmes, F.F.; Hearne III, E. (1979) A possible association of pernicious anemia with neoplasia. Oncology 36(3): 127-129	- Study design not relevant to this review protocol
Banks, Matthew, Graham, David, Jansen, Marnix et al. (2019) British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 68(9): 1545-1575	- Guideline
BIRD, R M (1953) Detection of carcinoma of the stomach in patients with pernicious anemia. Southern medical journal 46(5): 434-9	- Review article but not a systematic review
BOON, T H, SCHADE, R O, MIDDLETON, G D et al. (1964) AN ATTEMPT AT PRESYMPTOMATIC DIAGNOSIS OF GASTRIC CARCINOMA IN PERNICIOUS ANAEMIA. Gut 5: 269-70	- Study design not relevant to this review protocol
Borch, K (1986) Epidemiologic, clinicopathologic, and economic aspects of gastroscopic screening of patients with pernicious anemia. Scandinavian journal of gastroenterology 21(1): 21-30	- Data not reported in an extractable format or a format that can be analysed
Borch, K and Liedberg, G (1984) Prevalence and incidence of pernicious anemia. An evaluation for gastric screening. Scandinavian journal of gastroenterology 19(2): 154-60	- Study design not relevant to this review protocol
Bresky, G, Mata, A, Llach, J et al. (2003) Endoscopic findings in a biennial follow-up program in patients with pernicious anemia. Hepato-gastroenterology 50(54): 2264-6	- Study design not relevant to this review protocol
Brinton, L A, Gridley, G, Hrubec, Z et al. (1989) Cancer risk following pernicious anaemia. British journal of cancer 59(5): 810-3	- Study design not relevant to this review protocol
Elsborg, L; Andersen, D; Bastrup-Madsen, P (1973) Gastrocamera screening in pernicious anaemia. With special reference to the occurrence of gastric polyps and cancer.	- Study design not relevant to this review protocol

Study	Code [Reason]
Scandinavian journal of gastroenterology 8(1): 5-8	
Elsborg, L, Andersen, D, Myhere-Jensen, O et al. (1977) Gastric mucosal polyps in pernicious anaemia. Scandinavian journal of gastroenterology 12(1): 49-52	- Study design not relevant to this review protocol
Hsing, A W, Hansson, L E, McLaughlin, J K et al. (1993) Pernicious anemia and subsequent cancer. A population-based cohort study. Cancer 71(3): 745-50	- Study design not relevant to this review protocol
Hughes, Jing W, Muegge, Brian D, Tobin, Garry S et al. (2017) HIGH-RISK GASTRIC PATHOLOGY AND PREVALENT AUTOIMMUNE DISEASES IN PATIENTS WITH PERNICIOUS ANEMIA. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 23(11): 1297-1303	- Study design not relevant to this review protocol
Jordan, Paul H Jr; Barroso, Alberto; Sweeney, John (2004) Gastric carcinoids in patients with hypergastrinemia. Journal of the American College of Surgeons 199(4): 552-5	- Study design not relevant to this review protocol
Kokkola, A, Sjoblom, S M, Haapiainen, R et al. (1998) The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anaemia. A prospective follow-up study. Scandinavian journal of gastroenterology 33(1): 88-92	- Study design not relevant to this review protocol
Lahner, Edith, Hassan, Cesare, Esposito, Gianluca et al. (2017) Cost of detecting gastric neoplasia by surveillance endoscopy in atrophic gastritis in Italy: A low risk country. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 49(3): 291-296	- Study design not relevant to this review protocol
Lehtola, J.; Karttunen, T.; Krekela, I. (1985) Gastric carcinoids with minimal or no macroscopic lesion in patients with pernicious anemia. Hepato-Gastroenterology 32(2): 72-76	- Study design not relevant to this review protocol
Schafer, L W, Larson, D E, Melton, L J 3rd et al. (1985) Risk of development of gastric carcinoma in patients with pernicious anemia: a population-based study in Rochester, Minnesota. Mayo Clinic proceedings 60(7): 444-8	- Study design not relevant to this review protocol
Sjoblom, S M; Sipponen, P; Jarvinen, H (1993) Gastroscopic follow up of pernicious anaemia patients. Gut 34(1): 28-32	- Duplicate reference
Sjoblom, S.M.; Sipponen, P.; Jarvinen, H. (1993) Gastroscopic follow up of pernicious anaemia patients. Gut 34(1): 28-32	- Review article but not a systematic review
Stockbrugger, R W, Menon, G G, Beilby, J O et al. (1983) Gastroscopic screening in 80 patients with pernicious anaemia. Gut 24(12): 1141-7	- Study design not relevant to this review protocol
Ye, W and Nyren, O (2003) Risk of cancers of the oesophagus and stomach by histology or	- Study design not relevant to this review protocol

Study	Code [Reason]
subsite in patients hospitalised for pernicious anaemia. Gut 52(7): 938-41	

1

2 **Health Economic studies**

3 None.

4

Appendix K – Research recommendations – full details

K.1 Research recommendation

What monitoring should be offered to people with autoimmune gastritis (also known as pernicious anaemia) to identify gastric cancer?

K.1.1 Why this is important

People with autoimmune gastritis have and an increased risk of gastric adenocarcinoma and gastric neuroendocrine tumours compared with the general population. There is insufficient evidence to determine the type and extent of monitoring for gastric cancer that leads to the best outcomes for people with autoimmune gastritis.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	By comparing outcomes of patients undergoing different monitoring for gastric cancer, the most clinically effective strategy can be established and recommended in future guideline updates.
Relevance to NICE guidance	High: the research is essential to inform future updates of key recommendations in the guidance.
Relevance to the NHS	The outcome would affect the type and frequency of monitoring for gastric cancer being offered by the NHS to those with autoimmune gastritis.
National priorities	Not applicable
Current evidence base	Minimal data based on small, mixed (previous gastric surgery) samples. Evidence for gastroscopic monitoring is based on outdated gastroscopic techniques. No evidence was identified for barium meal, pepsinogen, gastrin, or combinations of pepsinogen and gastrin protocols.
Equality considerations	None known

K.1.3 Modified PICO table

Population	People with diagnosed autoimmune gastritis Stratify by: • People with any previous gastric surgery, including bariatric surgery
Intervention	Monitoring for gastric cancer: • Gastroscopy • Barium meal • Pepsinogen (followed by gastroscopy for those at high risk) • Gastrin (followed by gastroscopy for those at high risk) • Combined pepsinogen + gastrin (followed by gastroscopy for those at high risk)

Comparator	• All monitoring strategies compared with each other (including frequency of monitoring) • No monitoring

Outcome	• Mortality
	• Quality of life
	• Diagnosis of cancer
	• Stage of cancer at diagnosis/surgical resectability
	• Incidence of gastric neuroendocrine tumours (AKA carcinoid tumours/NETS/NENS)
	• Adverse events (procedure related):
	  ○ bleeding
	  ○ perforation
	  ○ aspiration

Study design	Randomised controlled trial
Timeframe	Long term
Additional information	None