Appendix C: Review protocols, searches and summary of modified GRADE [update 2014]

C.1 Review protocols

Table 1: Review question 1

	Details
Review question	When should (and with what indications) patients with uninvestigated dyspepsia be referred for endoscopy for further investigation and review of treatment plan?
Objectives	To identify which patients with uninvestigated dyspepsia need endoscopy for further investigation, to review disease progression or to monitor treatment plan.
Language	English only.
Study design	No restriction but exclude case series, case reports and qualitative studies.
Status	Published papers (full text only).
Population	Include • Dyspepsia • Functional dyspepsia • GORD symptoms • Heartburn • Chest pain • Epigastric pain • Upper abdominal pain • Reflux • Hypergastrinaemia • Ulcer • persistent symptoms Exclude • Patients <18 years • Endoscopically confirmed GORD, Ulcer dyspepsia, or confirmed functional dyspepsia at baseline Previous endoscopy within last year.
Intervention/ indications	Include For 'endoscopy' • Endoscopy

	• Flexible endoscopy • Gastroscopy • Videoscopic. • Natural Orifice endoscopy • Upper gastrointestinal (GI) endoscopy • high resolution endoscopy • oesophago-gastro-duodenoscopy (OGD) For 'signs, symptoms' • Dyspepsia • Functional dyspepsia • GORD symptoms • Heartburn • Chest pain • Epigastric pain • Upper abdominal pain • Reflux • Hypergastrinaemia • persistent symptoms • 'signs and symptoms' • 'severity' For 'risk factors' • Duration of symptoms (perhaps categorized) • Previous Hiatus hernia / sliding hernia • Eructation • Widened gastro oesophageal junction • 'Risk factors' • Diet • Smoking • Alcohol consumption • BMI / fat distribution / waist – hip ratio • Age • Sex • Ethnicity • Familial history • Single nucleotide polymorphism SNP • 'Nottingham scale' • Previous / Paediatric reflux surgery Note: Classification for 'signs & symptoms' and 'risk factors' may overlap <u>Exclude</u> • Endosonography/ultrasound Capsule endoscopy.

Control	• No endoscopy • Delayed endoscopy
Outcomes	• Heath related QOL (using disease specific tools) • Resolution of symptoms (Critical?) • Adverse events (Bleeding, oesophageal perforation, pneumothorax, anxiety) • Mortality • Medication use – frequency/dose • GP / hospital visits (resource use) • Change to diagnosis and subsequent management **(Critical).** • New diagnosis • Patient satisfaction/preferences. •
Other criteria for inclusion/exclusion of studies	Include • Patients with newly onset signs/symptoms • Primary care setting or patients referred to secondary care for endoscopy Exclude • Patients with previous Endoscopy within 1 year • Non English Language studies • Abstract only studies. •
Search strategies	No restriction but exclude case series, case reports and qualitative studies.
Review strategies	• The NICE methodology checklist for intervention or prognostic studies will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements.
Identified key studies	Studies Edenholm M et al (1985). Endoscopic findings in patients with ulcer-like dyspepsia. Scand J Gastroenterol Suppl. 1985;109:163-7 Rabeneck L, Wristers K, Souchek J, et al (2003). Impact of upper endoscopy on satisfaction in patients with previously uninvestigated dyspepsia. Gastrointest Endosc 2003;57:295-9 Quadri A, Vakil N (2003). Health-related anxiety and the effect of open-access endoscopy in US patients with dyspepsia. Aliment Pharmacol Ther 2003;17:835-40.

6 **Table 2: Review question 2**

	Details
Review question	What characteristics/symptoms of GORD or symptoms suggestive of GORD indicate endoscopy to exclude Barrett's oesophagus?
Objectives	To determine which risk factors are associated with development of Barrett's oesophagus in order to stratify which patients should be prioritized for endoscopy. Risk factors will encompass signs and symptoms.
Language	English only.
Study design	Longitudinal studies, cross sectional studies, case control studies, cohort studies, prognostic studies.
Status	Published papers (full text only).
Population	Adults (18 years and older) <u>Include</u> • Histological confirmed Barrett's oesophagus • Metaplasia/specialised intestinal metaplasia • Dyplasia (high and low grade) • Columnar epithelium <u>Exclude</u> • Existing/prevalent cancer • Neoplasia • Patients with previous surgery. Laparoscopic, or endoscopic treatment for Barrett's oesophagus • Barrett's oesophagus diagnosed on endoscopic appearance alone.
Intervention/ indications	<u>Include</u> • Duration of symptoms (perhaps categorized) • Hiatus hernia / sliding hernia • Eructation • Symptoms (chest pain, heartburn, GORD) • Severity • Widened gastro oesophageal junction • 'Risk factors' • Signs • Diet • Smoking • Alcohol consumption • BMI / fat distribution / waist – hip ratio • Age • Sex • Ethnicity • Familial history • Single nucleotide polymorphism SNP

	• 'Nottingham scale' • Previous / Paediatric reflux surgery <u>Exclude</u> • 24 hr pH monitoring • Bilitec • Previous Endoscopy • Histology • Biochemical markers (FASN enzyme, activated apoptotic naive and memory T cells, serum gastrin level, keratin 7 (KRT7), keratin 20 (KRT20), caudal type homeobox 2 (CDX2), mucin 2 oligomeric mucus/gel-forming (MUC2), tumor protein p53 (TP53) etc) • Other factor requiring endoscopy / biopsy to assess.
Control	Not applicable to prevalence question

Outcomes	• Proportion with positive diagnosis of Barrett's oesophagus • Size/length of Barrett's oesophagus.
Other criteria for inclusion/exclusion of studies	Include • Studies that report outcomes in multivariate analysis • Prospective studies Exclude • Studies analyzed using univariate analysis only • Prevalence studies for existing carcinoma • Studies reporting outcomes of treatment for Barrett's oesophagus • Surveillance of patients with Barrett's oesophagus for progression • Population screening studies.
Search strategies	Systematic reviews and primary prognostic studies.
Review strategies	• Study quality will be evaluated using the NICE prognostic checklist • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements.
Identified key studies	Kuo CJ (2010). Frequency and risk factors for Barrett's esophagus in Taiwanese patients: a prospective study in a tertiary referral center. Digestive Diseases & Sciences. 55(5):1337-43, 2010 Xiong LS (2010). Prevalence and risk factors of Barrett's esophagus in patients undergoing endoscopy for upper gastrointestinal symptoms. Journal of Digestive Diseases. 11(2):83-7, 2010 Anderson LA (2007). Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World J Gastroenterol. 2007 Mar 14;13(10):1585-94 Stein DJ (2005). The association of body mass index with Barrett's oesophagus. Aliment Pharmacol Ther. 2005 Nov 15;22(10):1005-10 Anderson LA, Cantwell MM, Watson RG, Johnston BT, Murphy SJ, Ferguson HR, McGuigan J, Comber H, Reynolds JV, Murray LJ. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Gastroenterology. 2009 136:799-805. Cook MB, Shaheen NJ, Anderson LA, Giffen C, Chow WH, Vaughan TL, Whiteman DC, Corley DA.Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. Gastroenterology. 2012 142:744-53. Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, Leighton P,

	Quesenberry C, Rumore GJ, Buffler PA.Abdominal obesity and body mass index as risk factors for Barrett's esophagus. Gastroenterology. 2007 133:34-41.

7 **Table 3: Review question 3**

	Details
Review question	Which patient characteristics/clinical indicators/criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed GORD managed in primary care to a consultant led medical or surgical service (specialist services)?
Objectives	To provide guidance to primary care providers as to how to select which patients require referral for specialist services.
Language	English only.
Study design	No restriction (but will exclude case series, case reports, narrative review and qualitative study).
Status	Published papers (full text only).
Population	Adults (18 years and older) <u>Include*</u> • GORD/GERD • Dyspepsia (investigated/uninvestigated dyspepsia, non-ulcer dyspepsia, functional dyspepsia) • Peptic ulcer disease • Heartburn • Reflux (*populations covered – based on CG17 plus functional dyspepsia) PLUS other search terms • New onset symptoms (while on medication) • Persistent symptoms >1 month • Refractory • Symptomatic • Treatment failure • Long term self-care >10 years • Failed on trial of PPI and *H pylori* test and treat.
Intervention/ indications	<u>Include (search terms)</u> • Specialist • Consultant • Gastroenterologist • Upper GI surgery • Complications

	• Refractory • Escalate • Referral • Expert • Secondary • Tertiary • Hospital • Outpatient • Investigations <u>Exclude</u> • Primary care • GP • Endoscopy.
Control	N/A

Outcomes	Critical • Health related QOL • Resolution/improvement of Symptoms / VAS • Patient satisfaction Important • Medication use/dose • GP/Hospital visits • Heartburn (% of days free). •
Other criteria for inclusion/exclusion of studies	Include • Any study illustrates 'who' (patient characteristic, clinical indicators, criteria) should be managed outside primary care that resulted in better patient outcomes. Exclude • Studies where the healthcare structure is considerably different to the UK where upwards referral for specialist treatment is not comparable. •
Search strategies	No restriction on study design (but will exclude case series, case reports, narrative review and qualitative study).
Review strategies	• An appropriate NICE methodology checklist will be used as a guide to appraise the quality of individual studies, or a checklist adapted from other published source will be used • Data on all included studies will be extracted into evidence tables • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Narrative/qualitative synthesis of evidence may be required. •
Identified key studies	Systematic reviews None indentified Studies van Bommel MJJ (2001). Consultations and referrals for dyspepsia in general practice—a one year database survey. Postgrad Med J 2001;77:514-518 Jones RH (1993). Problems with implementing guidelines: a randomised controlled trial of consensus management of dyspepsia. Qual Health Care 1993;2:217-221 Flameling RD (2010). Different characteristics of patients with gastro-oesophageal reflux disease on their path through healthcare: a population follow-up study. European Journal of Gastroenterology & Hepatology May 2010 - Volume 22 - Issue 5 - pp 578-582 Gerson LB (2011). Development of a refractory gastro-oesophageal reflux score using an administrative claims database. Alimentary Pharmacology & Therapeutics 34(5):555-67, 2011 Sep.

8 **Table 4: Review question 4**

	Details
Review question	What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease? i) to control / reduce oesophagitis ii) as maintenance therapy.
Objectives	To compare different PPIs to see which is the most effective to reduce symptoms and reflux exposure.
Language	English only.
Study design	Systematic reviews/meta-analysis, RCTs (blind or open-label).
Status	Published papers (full text only).
Population	i) Adults (18 years and older) with endoscopically confirmed severe erosive reflux disease / GORD, and oesophagitis ii) Adults (18 years and older) with healed severe erosive reflux disease / GORD, and oesophagitis <u>Include</u> • Los Angeles classification grade C or D, Savary-Miller grade 3 or 4 <u>Exclude</u> • Los Angeles classification gradeA or B. Savary-Miller grade 1 or 2(not severe) or grade 5 (existing Barrett's oesophagus).
Intervention/ indications	To compare all PPIs vs Placebo or one another <u>Include</u> • Omeprazole • Rabeprazole (sodium) • Lansoprazole • Esomeprazole • Pantoprazole <u>Exclude</u> • Dexlansoprazole – not licensed in UK • H_2RAs (exclude from decision data set, but possibly use in comparison dataset in network analysis). •
Control	• Placebo • H_2RA • Existing self-care • (Each of the interventions listed in interventions box above will be

	compared to one another also).
Outcomes	• Endoscopic appearance/chance in LA grade/resolution of oesophagitis (dichotomous) • Health related QOL scales • Acid exposure time (% time <pH4 on 24 hour monitoring) • Progression to Barrett's oesophagus or carcinoma • Adverse events (headache, diarrhoea, nausea, drug interactions, metallic taste, rash) • Mortality • Hypergastro-anaemia.
Other criteria for inclusion/exclusion of studies	Include • Studies comparing the above listed treatment regimens • >30-days follow-up period Exclude • Non-randomised studies, observational studies; and studies not published full-text (i.e. conference abstracts); or systematic reviews that contain any of these types of studies • Studies with mixed populations (i.e. some patients within the study population who are not grade C or D) will only be included if outcomes are clearly separated for these groups • <7 days regimens • <30 day follow up • Studies assessing pharmacological therapies other than, PPIs • Studies using unlicensed drugs in both / all arms of the trial • Dose ranging studies • Studies which consider PPI plus alginate vs PPI alone.
Search strategies	Systematic reviews/meta-analysis, RCTs, quasi-RCTs.
Review strategies	• The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis) • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements • Sub group analyses will be undertaken for different dose and duration of treatment, and for populations with a definitive grade of oesophagitis C or D vs non definitive populations.
Identified key studies	Systematic reviews Edwards SJ et al (2006). Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis – a comparison of esomeprazole and other PPIs. Alimentary Pharmacology & Therapeutics 2006 24: 743-750

	McDonagh MS, Carson S, Thakurta S (2009). Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 Portland (OR). Oregon Health & Science University 2009 May RCTs (some included in reviews above) Fennerty MB, Johanson JF, Hwang C, et al (2005). Efficacy of esomeprazole 40mg versus lansoprazole 30mg for healing moderate to severe erosive esophagitis. Aliment Pharmacol Ther 2005; 21: 455–63 Schmitt C (2006). A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40mg) and omeprazole (20mg) for the treatment of erosive esophagitis. Dig Dis Sci. 2006 May;51(5):844-50 Lightdale CJ (2006). A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20mg) and standard-dose omeprazole (20mg) in patients with erosive esophagitis. Dig Dis Sci. 2006 May;51(5):852-7.

9 **Table 5: Review question 5i**

	Details
Review question	In patients with symptoms of dyspepsia who are positive for *Helicobacter pylori*, which eradication regimens are the most clinically effective in the eradication of *H pylori?*
Objectives	To compare different regimens to see which is the most effective in the eradication of *H pylori.*
Language	English only.
Study design	Systematic reviews/meta-analysis, RCTs (blind or open-label).
Status	Published papers (full text only).
Population	Adults (18 years and older) with: • Symptoms of dyspepsia • Positive test for *H pylori* • Naïve to previous antibiotic treatment Include • Univestigated dyspepsia • Ulcer dyspepsia (gastric or peptic) • Functional/non ulcer dyspepsia Can consider together for analysis – same risk associated with failure Exclude • Studies with patients with *H pylori* infection being treated for diagnosis other than dyspepsia - gastric cancer, NSAID related GI irritation, or population

	screening. • Studies where *H pylori* has not been confirmed (i.e. studies in high prevalence areas where infection is assumed) • Confirmed GORD • Exclude studies conducted outside of Northern Europe or Germany, USA or Canada which included clarithromycin or levofloxacin as the intervention or comparator. • Exclude studies conducted within Africa and Asia which included metronidazole as the intervention or comparator.
Intervention/ indications	Comparison of the effectiveness of the following interventions – all compared to each other A) SEQUENTIAL THERAPY B) TRIPLE THERAPY C) QUADRUPLE THERAPY WITH BISMUTH D) QUARDUPLE THERAPY WITH THREE ANTIBIOTICS We will include 'Individual/named antibiotics' in two classes (Penicillins and Macrolides) but assume a class effect in all others <u>Include</u> • Studies comparing different lengths of the above listed regimens • Follow up period to be a minimum of one month after treatment <u>Exclude</u> • Regimens using two or more of the same class of antibiotics • Quadruple with bismuth, 3 antibiotics, and no acid suppressant • Quadruple with 2 antibiotics and 2 acid suppressants • <7 days regimens.
Control	• Placebo • Mono therapy • Dual therapy • Sequential/Triple/Quad therapy with H2RA as acid suppressant • Triple therapy with no acid suppressant (with or without bismuth) • Sequential/Triple/Quad therapy with off-label antibiotic included • Each of the interventions will be compared to one another also.

Outcomes	Critical • Eradication rate • Adherence to medication Important • Adverse events • Mortality • Antibiotic resistance rates (if reported) • Health-related quality of life (using generic or disease-specific tools).
Other criteria for inclusion/exclusion of studies	Include • Studies with mixed populations (i.e. patients who have and have not tested positive for *H pylori*) will only be included if outcomes are clearly separated between these groups. Exclude • 2nd line treatment (this will be covered in another question) • Non-randomised studies, observational studies; and studies not published full-text (i.e. conference abstracts); or systematic reviews that contain any of these types of studies • Mono or dual therapy (except for use in network meta-analysis) • Regimens/therapies which include H2RA as acid suppressant (except as comparator dataset) • Non-pharmacological therapies (i.e. herbal, probiotics) • Studies assessing pharmacological therapies other than antibiotics, PPIs, H2RAs, chelates and complexes such as bismuth or sucralfate • Studies using unlicensed drugs in all arms of the trial • Studies using off-label drugs in all arms for 1st line • Studies comparing the effectiveness of cytoprotective or mucolytic agents • Quadruple therapy with 2 antibiotics and H2RAs (exclude for 1st line only).
Search strategies	Systematic reviews/meta-analysis, RCTs, quasi-RCTs.
Review strategies	The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies Data on all included studies will be extracted into evidence tables Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis) All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements Sub group analyses will be undertaken for the underlying cause of dyspepsia where appropriate.
Identified key studies	Systematic reviews • Chen Y, Wu LH, He XX (2009). Sequential therapy versus standard triple therapy for Helicobacter pylori eradication in Chinese patients: a meta-analysis (Provisional abstract). World Chinese Journal of Digestology 17 (32) 3365-3369.2009 • Ford AC, Malfertheiner P, Giguere M, Santana J, Khan M, Moayyedi P (2008). Adverse events with bismuth salts for Helicobacter pylori eradication: systematic review and meta-analysis (Structured abstract). World Journal of

	Gastroenterology 14 (48) 7361-7370.2008 • Gatta L, Vakil N, Leandro G, Di Mario F, Vaira, D (2009). Sequential therapy or triple therapy for Helicobacter pylori infection: systematic review and meta-analysis of randomized controlled trials in adults and children (Structured abstract). American Journal of Gastroenterology 104 (12) 3069-3079.2009 • Gisbert JP, Nyssen OP, McNicholl AG, Megraud F, Savarino V, Oderda G, Fallone C, Fischbach L, Bazzoli F (2011). Sequential versus standard triple therapy for Helicobacter pylori eradication Cochrane Database of Systematic Reviews (3) 2011 • Tong JL, Ran ZH, Shen J, Xiao SD (2009). Sequential therapy vs. standard triple therapies for Helicobacter pylori infection: a meta-analysis (Structured abstract). Journal of Clinical Pharmacy and Therapeutics 34 (1) 41-53.2009 <u>RCTs (some included in reviews above)</u> • Malfertheiner et al (2011). Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. Lancet 377: 905–13 • Fischbach L, Evans EL (2007). Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for Helicobacter pylori. Aliment Pharmacol Ther 2007;26:343–57 • Jafri NS, Hornung CA, Howden CW (2008). Meta-analysis: sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment. Ann Intern Med 2008;148:923–31 • Vaira D, Zullo A, Vakil N, et al (2008). Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial. Ann Intern Med 2007;146:556–63 • Wu DC, Hsu PI, Wu JY, et al (2008). Randomized controlled comparison of sequential and quadruple (concomitant) therapies for *H pylori* infection. Gastroenterology 2008;134:137.

10 **Table 6: Review question 5ii**

	Details
Review question	What *H pylori* eradication regimens should be offered as second-line treatments when first-line treatments fail?
Objectives	To compare different regimens to see which is the most effective second-line regimen for the eradication of *H pylori* when first-line treatments fail.
Language	English only.
Study design	Systematic reviews/meta-analysis, RCTs (blind or open-label).
Status	Published papers (full text only).

Population	Adults (18 years and older) who have: • Symptoms of dyspepsia • Positive test for *H pylori* • Failed the first line eradication regimen recommended in Q5i <u>Include</u> • Univestigated dyspepsia • Ulcer dyspepsia (gastric or peptic) • Functional/non ulcer dyspepsia Can consider together for analysis – same risk associated with failure <u>Exclude</u> • Studies with patients with *H pylori* infection being treated for diagnosis other than dyspepsia - gastric cancer, NSAID related GI irritation, or population screening. • Studies where *H pylori* has not been confirmed (i.e. studies in high prevalence areas where infection is assumed) • Endoscopically confirmed GORD • Studies where 2nd line treatment was commenced within one month following completion of 1st line treatment.
Intervention/ indications	Comparison of the effectiveness of the following interventions – all compared to each other SEQUENTIAL THERAPY TRIPLE THERAPY • Ab x 2 + PPI • Ab x 1 + PPI + Bis • Ab x 2 + H2RA • Ab x 1 + H2RA + Bis QUADRUPLE THERAPY WITH BISMUTH • Ab x 3 + Bis • Ab x 2 + PPI + Bis • Ab x 2 + H2RA + Bis QUARDUPLE THERAPY WITH THREE ANTIBIOTICS • Ab x 3 + PPI • Ab x 3 + H2RA We will include 'Individual/named antibiotics' in two classes (Penicillins and Macrolides) but assume a class effect in all others <u>Include</u> • Studies comparing different lengths of the above listed regimens • Follow up period to be a minimum of one month after treatment

	Exclude • Regimens using two or more of the same class of antibiotics • <7 days regimens • Exclude studies where the 2nd line regimen is a repeat of the 1st line regimen • Exclude studies where the 2nd line regimen includes antibiotics from the same class in all arms as used in the 1st line regimen (for clarithromycin and quinolones only).

Control	Include
	• SEQUENTIAL THERAPY
	• MONOTHERAPY
	  ○ Ab alone
	  ○ PPI alone
	  ○ H2RA alone
	• DUAL THERAPY
	  ○ Ab x 2
	  ○ Ab x 1 + PPI
	  ○ Ab x 1 + H2RA
	• TRIPLE THERAPY
	  ○ Ab x 3
	  ○ Ab x 2 + H2RA
	  ○ Ab x 1 + H2RA + Bis
	• QUADRUPLE THERAPIES
	  ○ Ab x 4
	  ○ Ab x 3 + H2RA
	  ○ Ab x 3 + Bis
	  ○ Ab x 2 + H2RA + Bis
	
	Sequential / Triple / Quad therapy with off-label antibiotic included
	Each of the interventions will be compared to one another.

Outcomes	Critical • Eradication rate • Adverse events Important • Effect on symptoms • Adherence to medication • Recurrence rate • Eradication by resistance status.
Other criteria for inclusion/exclusion of studies	Include • Studies with mixed populations (i.e. patients who have and have not tested positive for *H pylori*) will only be included if outcomes are clearly separated between these groups • Studies using off-label drugs in all arms for 2nd line Exclude • 1st line treatment (this will be covered in another question) • Studies where 1st line eradication regimen is not detailed clearly/not given or a mixed population (i.e. patients have received a mixture of 1st line regimens and outcomes are not separated for these groups) and studies where the regimen was not explicit (e.g. class information given but no specific information about drug/antibiotic) • Non-randomised studies, observational studies; and studies not published full-text (i.e. conference abstracts); or systematic reviews that contain any of these types of studies • Non-pharmacological therapies (i.e. herbal, probiotics) • Studies assessing pharmacological therapies other than antibiotics, PPIs, H2RAs, chelates and complexes such as bismuth or sucralfate • Studies using unlicensed drugs in all arms of the trial • Studies comparing the effectiveness of cytoprotective or mucolytic agents • Any trial where patients are not randomized to 2nd line therapy • Studies where patients had received more than one previous attempt at eradication • Studies where drugs were given on sensitivity analysis.
Search strategies	Systematic reviews/meta-analysis, RCTs.
Review strategies	• The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis) • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements • Sub group analyses will be undertaken for the underlying cause of dyspepsia where appropriate.
Identified key studies	Systematic reviews • Gisbert JP, Morena F (2006) Systematic review and meta-analysis:

	levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. Alimentary Pharmacology & Therapeutics 23: 35-44. RCTs • Cheng H, Hu FL (2009) Furazolidone, amoxicillin, bismuth and rabeprazole quadruple rescue therapy for the eradication of Helicobacter pylori. World Journal of Gastroenterology 15: 860-4. • Chung JW, Lee JH, Jung HY et al. (2011) Second-line Helicobacter pylori eradication: a randomized comparison of 1-week or 2-week bismuth-containing quadruple therapy. Helicobacter 16: 289-94. • Gisbert JP, Gisbert JL, Marcos S et al. (2008) Empirical rescue therapy after Helicobacter pylori treatment failure: a 10-year single-centre study of 500 patients. Alimentary Pharmacology & Therapeutics 27: 346-54.

11 **Table 7: Review quesiton 6**

	Details
Review question	What is the effectiveness of laparoscopic fundoplication compared to medical management in patients with GORD?
Objectives	To compare whether keyhole surgery or drug management is better for patients with heartburn and or reflux symptoms.
Language	English only.
Study design	RCTs, Quasi RCTs, systematic reviews.
Status	Published papers (full text only).
Population	• GORD/GERD/REFLUX • Heartburn • Acid exposure/indigestion • Waterbrash • Oesophagitis • With positive test for reflux (pH monitoring/manometry/ doscopy) Include • Patients with symptoms >1year • Patients with stable symptoms for >3months (without change in medication) • Patients with symptoms expected to continue for 2 years Subgroup/sensitivity analysis Treatment naïve patients (if data are available) Exclude • Patients <18 years • Previous Surgery for GORD, or oesophogastirc surgery • Patients with GORD and high grade dysplasia.

Intervention/ indications	Include • Laparoscopic Fundoplication (either total/full , partial, or floppy) • Nissen • Anti reflux surgery Subgroup/sensitivity analysis Total/full fundoplication vs other techniques (if data are available) Exclude • Open (Nissen) fundoplication • Endoscopic ablative procedures • Other minimally invasive surgical procedures.
Control	Include • Medical therapy with PPIs as at least one element of treatment • Esopmenprazole • Lamsoprazole • Omeprazole • Pantoprazole • Raberazole Sodium Exclude • Studies with H_2RAs (histamine receptor agonists) only (monotherapy) • Antacids • Other surgery.

Outcomes	• Health related QOL • Symptom control – dichotomous outcome • Acid reflux – 24 hr pH monitoring (% time <4) • Mortality • Medication use – frequency/dose • Serious adverse event – Bleeding, perforation, pneumothorax, dysphagia.
Other criteria for inclusion/exclusion of studies	Include • Robotic Laparoscopic – but treat same as 'human' laparoscopic (Interventional Procedures programme has concluded that these are in effect the same class of intervention) Exclude • Studies with follow up <1 year • Allocation by patient preference • Allocation by case selection • Studies of surgery vs sham surgery.
Search strategies	RCTs, Quasi RCTs, systematic reviews.
Review strategies	• The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Dichotomous data will be pooled as relative risk and 95% CI if there is sufficient data • Adverse effects (incidence rates) will be pooled as relative risk and 95% CI • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Sub group analysis for those with refractory / chronic GORD only vs mixed GORD population will be undertaken where appropriate.
Identified key studies	Systematic reviews Broeders JA (2010). Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. British Journal of Surgery 97 (9) 1318-1330.2010 Catarci M (2004). Evidence-based appraisal of antireflux fundoplication. Annals of Surgery 239 (3) 325-337.2004 Chang EY (2007.) The effect of antireflux surgery on esophageal carcinogenesis in patients with Barrett esophagus: a systematic review. Annals of Surgery 246 (1) 11-21.2007 Markar SR(2010). Robotic vs laparoscopic Nissen fundoplication for gastro-

	oesophageal reflux disease: systematic review and meta-analysis (Provisional abstract). International Journal of Medical Robotics and Computer Assisted Surgery 6 (2) 125-131.2010 Peters MJ (2009). Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. American Journal of Gastroenterology 104 (6) 1548-1561.2009 Rees JRE (2010.) Treatment for Barrett's oesophagus. Cochrane Database of Systematic Reviews (1) 2010. Varin O (2009). Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Archives of Surgery 144 (3) 273-278.2009 Wileman SM (2010). Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database of Systematic Reviews (3) 2010 <u>Studies</u> Grant A (2008). The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease - a UK collaborative study. The REFLUX Trial. Health Technology Assessment 1-2008 Anvari M (2006). A randomised controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: one year follow-up. Surgical Innovation 2006;13(4):238–49. Attwood SE (2008. Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience. Journal of Gastrointestinal Surgery 2008a; 12:1646–55. Cookson R (2005). Short-term cost effectiveness and long-term cost analysis comparing laparoscopic Nissen fundoplication with proton pump inhibitor maintenance for gastro-oesophageal reflux disease. British Journal of Surgery 2005;92(6):700–6.

12 **Table 8: Review question 7**

	Details
Review question	What other management is effective for patients who do not respond to PPIs, H2 receptor antagonists, or *H pylori* eradication despite optimum primary care, or patients who have relapsed following surgery?
Objectives	To compare whether additional specialist medical management interventions are better than usual care for patients with refractory heartburn and or reflux symptoms.
Language	English only.

Study design	RCTs, Quasi RCTs, systematic reviews, observational studies, cohort studies, case control studies.
Status	Published papers (full text only).
Population	Include • GORD / GERD / REFLUX • Heartburn • Acid exposure • Oesophagitis • Dyspepsia • Upper abdominal pain AND/PLUS • On 40mg dose PPI bd/ H2RA • Patients with symptoms for >1 month • Refractory • Treatment failure • Relapse • Symptomatic • Specialist • Secondary care • Consultant • Hospital • Secondary care Exclude Patients <18 years H2RA or PPI or *H pylori* eradication treatment naïve patients.
Intervention/ indications	Include • Split dose PPI • Nocturnal dose PPI • Dual/combination therapy PPI plus H2RA treatment • Prokinetics/dopamine receptor antagonists (metoclopramide, domperidone, itopride, mosapride) • Laparoscopic (Nissen) fundoplication Exclude • Low dose antidepressants Tricyclics (and related) • Low dose antidepressants Monoamine-oxidase inhibitors • Low dose antidepressants SSRIs • Low dose antidepressants others, Venlafaxine Tryptophan, Reboxetine, Mirtazapine, flupentixol, Duloxetine, Agomelatine) • Muscle relaxants (Baclofen, R-Baclofen, GABA Agonist, 5HT4 antagonist) • Pain modifiers

	Standard pharmacological regimens.
Control	Include • Standard pharmacological interventions • No intervention • Self treatment.

Outcomes	Critical • Health related QOL • Heartburn (% days free) • Remission of symptoms (dichotomous outcome) Important • Acid reflux – 24 hr pH monitoring (% time <4) • Mortality • Adverse events (specific to each sub-question).
Other criteria for inclusion/exclusion of studies	Include • UK or Developed world setting • Crossover trials Exclude • Studies with follow up <6 months • Allocation by patient preference • Allocation by case selection.
Search strategies	RCTs, Quasi RCTs, systematic reviews, observational studies, cohort studies, case control studies.
Review strategies	• The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect using direct comparisons • Dichotomous data will be pooled as relative risk and 95% CI if there is sufficient data • Adverse effects (incidence rates) will be pooled as relative risk and 95% CI • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Sub group analysis for those with refractory / chronic GORD only vs mixed GORD population will be undertaken where appropriate.
Identified key studies	Systematic reviews Pan T, Wang Y, Guo Z, Wang Q (2004). Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough Studies (these may be included within the systematic reviews listed above) Janiak P, Thumshirn M, Menne D, Fox M, Halim S, Fried M at al (2007). Clinical trial: the effects of adding ranitidine at night to twice daily omeprazole therapy on nocturnal acid breakthrough and acid reflux in patients with systemic sclerosis-a randomized controlled cross-over trial. Alimentary Pharmacology and Therapeutics 2007; 26(9):1259-65 Khoury RM, Katz PO, Hammod R, Castell DO (1999). Bedtime ranitidine does

	not eliminate the need for a second daily dose of omeprazole to suppress nocturnal gastric pH. Alimentary Pharmacology and Therapeutics 1999; 13(5):675-678 Vakil, N, Guda N, Partington S (2006) .The effect of over-the-counter ranitidine 75 mg on night-time heartburn in patients with erosive oesophagitis on daily proton pump inhibitor maintenance therapy. Alimentary Pharmacology & Therapeutics 23(5), 649-653.

13 **Table 9: Review question 8**

	Details
Review question	Should surveillance be used for patients with Barrett's oesophagus to detect progression to cancer, and improve survival?
Objectives	To compare structured endoscopic surveillance vs ad hoc endoscopy as required (no surveillance programme) in patients with Barrett's to identify progression to cancer.
Language	English only.
Study design	RCTs, systematic reviews, non randomised comparative studies, historically controlled studies (before and after), case control studies, cohort studies, case series.
Status	Published papers (full text only).
Population	<u>Include</u> • Barrett's oesophagus • Metaplasia/intestinal metaplasia • Dyplasia • Neoplasia • Columnar AND epithelium/metaplasia • Minimum length / distance from gastro-esophageal junction • Histologically positive • Precancer • Goblet cells • Mucosal inflammation • Long/short AND segment Minimum length of time since diagnosis with Barrett's 6 months <u>Exclude</u> • Patients <18 years • Previous Surgery for GORD or oesophogastirc surgery. • Previous surveillance programme • Alarm signs for referral • Other stratified patient cohort. • Carcinoma

	• Studies that do not provide endoscopic criteria for definition of BO.
Intervention/ indications	Include • Biopsy • Quadrant/circumferential • Surveillance • Monitoring • Endoscopy AND gastrointestinal • Repeat screening/mass screening • Protocol/programme Exclude • Surveillance endoscopy without biopsy. • Surveillance for the development of Barrett's • Non Quadrant samples • Samples taken >2cm intervals • Biopsy assessment for dysplasia by individual histo-pathologist/untrained pathologists • Surveillance less frequently than 3 years.
Control	Include Endoscopy as needed Spontaneous detection Incidental identification Ad hoc endoscopy No surveillance.

Outcomes	• Health related QOL – EQ 5D and SF-36 (EQ5D favoured, but I've found a few using SF-36) • GORD/Health related QOL (using disease specific tools) • Adverse event (Bleeding, oesophageal perforation, pneumothorax, anxiety) • Mortality • Endoscopic appearance • Progression to andenocarcinoma and stage identified • GP visits.
Other criteria for inclusion/exclusion of studies	Include Superiority studies Non-inferiority studies Other treatment for Barrett's standardized in both arms – drugs doses Standardised treatment protocol for patients that develop high grade dyplasia or cancer (resection oesophagectomy, or ablative endoscopic techniques) Exclude Studies with follow up <3 years Studies with n<100.
Search strategies	RCTs, Quasi RCTs, systematic reviews, Non-randomised comparative studies, historically controlled studies (before and after), case control studies, cohort studies, case-series.
Review strategies	• The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Dichotomous data will be pooled as relative risk and 95% CI if there is sufficient data • Adverse effects (incidence rates) will be pooled as relative risk and 95% CI • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Sub group analysis for those with refractory/chronic GORD only vs mixed GORD population will be undertaken where appropriate.
Identified key studies	Systematic reviews NON RCT Jankowski JA (2002). Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. Gastroenterology. 122(2):588-90. Studies NON RCT MacDonald CE (2000). Final results from 10 year cohort of patients undergoing

	surveillance for Barrett's Oesophagus: observational study. BMJ 321:1252-5. Murray L (2003). Risk of adenocarcinoma in Barrett's oesophagus: population based study. BMJ 327; 534-5.

C.2 IS search strategies

C.2.1 Scoping searches

Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in September 2011 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

Guidelines/website	Systematic review/economic evaluations
• Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland • Audit Commission • British Association of Paediatric Endoscopic Surgeons • British Society of Gastroenterology • British Society of Paediatric Gastroenterology, Hepatology and Nutrition • Campaign Against Reflux Disease (CARD) • Care Quality Commission • CORE Charity • Department of Health • European Helicobacter Study Group • Guidelines International Network (GIN) • Healthcare Improvement Scotland • Health Protection Agency • Joint Advisory Group on GI Endoscopy • King´s Fund • National Audit Office • National Patient Safety Agency • National Institute for Health and Clinical Excellence (NICE) - published & in development guidelines • National Institute for Health and Clinical Excellence (NICE) - Topic Selection • National Institute for Innovation and Improvement • National Patient Safety Agency • National Prescribing Centre • NHS Business Services Authority • NHS Evidence • NHS Information Centre • NHS Scotland • NHS Wales • New Zealand Guidelines Group	• BMJ Clinical Evidence • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Health Economic Evaluations Database (HEED) • Health Technology Assessment (HTA) Database • NHS Economic Evaluation Database (NHS EED) • NIHR Health Technology Assessment • NIHR Health Services and Delivery Research (HS&DR) Programme • Programme • TRIP Database •

• Oesophageal Patients Association • Primary Care Society for Gastroenterology • Prodigy (formerly Clinical Knowledge Summaries) • Reflux Advice.co.uk • Royal Colleges • Royal Pharmaceutical Society of Great Britain • Scottish Audit of Gastro-Oesophageal Cancer Steering Group • Scottish Intercollegiate Guidelines Network (SIGN) • Scottish Medicines Consortium • Social Care Institute for Excellence (SCIE) • US National Guideline Clearinghouse	

10.2.2 Main searches

Sources searched for the guideline

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

10.2.2.1 Identification of evidence for clinical questions

The searches were conducted between November 2011 and May 2013.The aim of the searches was to identify evidence for each of the clinical questions being asked.

The MEDLINE search strategies are presented below. These were translated for use in all of the other databases.

Review question 1:

What is the diagnostic utility of non-urgent endoscopy in patients with signs and symptoms of dyspepsia or GORD?

Database: Ovid MEDLINE(R) <1946 to May Week 1 2013> (update search conducted on 11 December 2013)

Search Strategy:

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1 exp Gastroesophageal Reflux/ (21027)

2 exp Duodenogastric Reflux/ (1565)

3 (reflux$ or gord or gerd or ger).tw. (39779)
4 Esophageal Sphincter, Lower/ (585)
5 lower esophageal sphincter.tw. (3304)
6 lower oesophageal sphincter.tw. (912)
7 (les or los).tw. (17380)
8 pyros$.tw. (3794)
9 acid exposure.tw. (1984)
10 Dyspepsia/ (7027)
11 (dyspep$ or indigestion$).tw. (10106)
12 (regurg$ or waterbrash$).tw. (25130)
13 hypergastrin*.tw. (1546)
14 Heartburn/ (1642)
15 heartburn$.tw. (3654)
16 exp Abdominal Pain/ (24380)
17 ((abdom$ or stomach$) adj3 (ache$ or pain$ or discomfort$)).tw. (36640)
18 Chest Pain/ (8711)
19 ((chest$ or thora$) adj3 (ache$ or pain$ or discomfort$)).tw. (24251)
20 (epigastri$ adj3 (ache$ or pain$ or discomfort$)).tw. (3381)
21 or/1-20 (179328)
22 exp Endoscopy, Digestive System/ (78303)
23 (endoscop$ or gastroscop$ or videoscop$).tw. (126962)
24 chromoendoscop$.tw. (532)
25 (esophagoscop$ or oesophagoscop$).tw. (1762)
26 or/22-25 (162901)
27 21 and 26 (19121)
28 risk factors/ (523427)
29 risk$.tw. (1123252)
30 "Signs and Symptoms"/ (422)
31 (sign* adj symptom*).tw. (3497)
32 or/28-31 (1317377)
33 27 and 32 (2631)
34 exp Hernia/ (59294)

75	35	(hernia$ or enterocele$).tw. (48720)
76	36	34 or 35 (72057)
77	37	27 and 36 (1244)
78	38	Eructation/ (280)
79	39	(eructat$ or belch$ or burp$).tw. (997)
80	40	38 or 39 (1110)
81	41	27 and 40 (126)
82	42	Polymorphism, Single Nucleotide/ (56558)
83	43	single nucleotide polymorphism.tw. (12097)
84	44	or/42-43 (59355)
85	45	27 and 44 (11)
86	46	((paediatric or pediatric) adj reflux$).tw. (9)
87	47	27 and 46 (1)
88	48	(famil* adj history).tw. (38268)
89	49	27 and 48 (137)
90 91	50	((gastro-oesophageal$ or gastrooesophageal$ or gastroesophageal$ or gastro-esophageal$) adj junction$).tw. (1923)
92	51	27 and 50 (331)
93	52	exp Diet/ (182864)
94	53	(diet$ or food$ or nutrition$).tw. (635091)
95	54	52 or 53 (698692)
96	55	27 and 54 (1151)
97	56	exp Smoking/ (115186)
98	57	(smok$ or cigarette$ or cigar$ or tobacco$).tw. (201167)
99	58	56 or 57 (228452)
100	59	27 and 58 (481)
101	60	exp Drinking Behavior/ (54011)
102	61	(alcohol$ or drink$).tw. (259963)
103	62	or/60-61 (271521)
104	63	27 and 62 (559)
105	64	body mass index/ (72094)
106	65	(body mass index$ or bmi$ or quetelet$ index$).tw. (110028)

66 Body Weight/ (156681)

67 exp Overweight/ (130992)

68 (weight$ or overweight$ or obes$ or body fat).tw. (727583)

69 or/64-68 (885805)

70 27 and 69 (1665)

71 Age Factors/ (358134)

72 Aging/ (180363)

73 Geriatrics/ (26146)

74 exp Aged/ (2211124)

75 Middle Aged/ (3144169)

76 (age$ or aging or elder$ or geriatric$ or old$).tw. (2842713)

77 or/71-76 (5532610)

78 33 and 77 (1944)

79 Sex/ (7197)

80 Sex Factors/ (202377)

81 Men/ (2535)

82 Women/ (13200)

83 (sex or sexes or gender$ or male$ or female$ or man or woman or women or men).tw. (2090224)

84 or/79-83 (2174250)

85 33 and 84 (883)

86 exp Population Groups/ (197033)

87 eh.fs. (115162)

88 (ethnic$ or ethno$ or race$ or racial$).tw. (155305)

89 or/86-88 (342359)

90 27 and 89 (278)

91 animals/ not humans/ (3753959)

92 33 or 37 or 41 or 45 or 47 or 49 or 51 or 55 or 59 or 63 or 70 or 78 or 85 or 90 (6383)

93 92 not 91 (6294)

94 limit 93 to english language (5150)

95 incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos:.tw. or predict:.tw. or course:.tw. (2070024)

96 (sensitiv: or diagnos:).mp. or di.fs. (3656151)

97 95 or 96 (5064379)

98 94 and 97 (3567)

Review Question 2:

Which risk factors indicate endoscopy in order to exclude Barrett's oesophagus?

Database: Ovid MEDLINE(R) <1946 to November Week 2 2012> (update search conducted on 12 December 2013.

Search Strategy:

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1 Barrett Esophagus/ (5715)

2 barrett$.tw. (6721)

3 ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4244)

4 or/1-3 (10763)

5 exp Endoscopy/ (238917)

6 (endoscop$ or gastroscop$ or videoscop$).tw. (124065)

7 chromoendoscop$.tw. (519)

8 (esophagoscop$ or oesophagoscop$).tw. (1758)

9 or/5-8 (287817)

10 4 and 9 (3856)

11 risk factors/ (508949)

12 risk$.tw. (1087586)

13 or/11-12 (1274619)

14 10 and 13 (1162)

15 exp Hernia/ (58747)

16 (hernia$ or enterocele$).tw. (47909)

17 15 or 16 (71245)

18 10 and 17 (365)

19 Eructation/ (277)

20 (eructat$ or belch$ or burp$).tw. (971)

21 19 or 20 (1080)

22 10 and 21 (12)

23 Chest Pain/ (8520)

24 ((chest or thora$) adj3 (pain$ or ache$ or discomfort$)).tw. (23936)

25 Heartburn/ (1544)

26 (heartburn$ or pyros$).tw. (6731)

27 or/23-26 (33421)

28 10 and 27 (308)

29 bile$ reflux$.tw. (683)

30 10 and 29 (40)

31 ((gastro-oesophageal$ or gastrooesophageal$ or gastroesophageal$ or gastro-esophageal$) adj junction$).tw. (1880)

32 10 and 31 (181)

33 exp Diet/ (178565)

34 (diet$ or food$ or nutrition$).tw. (619496)

35 33 or 34 (682299)

36 10 and 35 (78)

37 exp Smoking/ (113322)

38 (smok$ or cigarette$ or cigar$ or tobacco$).tw. (197081)

39 37 or 38 (224058)

40 10 and 39 (117)

41 exp Drinking Behavior/ (53005)

42 (alcohol$ or drink$).tw. (255109)

43 or/41-42 (266547)

44 10 and 43 (100)

45 body mass index/ (69217)

46 (body mass index$ or bmi$ or quetelet$ index$).tw. (105391)

47 Body Weight/ (155285)

48 exp Overweight/ (127354)

49 (weight$ or overweight$ or obes$ or body fat).tw. (710695)

50 or/45-49 (865676)

51 10 and 50 (184)

52 Age Factors/ (353281)

53 Aging/ (177973)

54 Geriatrics/ (26016)

55 exp Aged/ (2177675)

56 Middle Aged/ (3096169)

57 (age$ or aging or elder$ or geriatric$ or old$).tw. (2782636)

58 or/52-57 (5441703)

59 14 and 58 (688)

60 Sex/ (7245)

61 Sex Factors/ (198826)

62 Men/ (2516)

63 Women/ (13143)

64 (sex or sexes or gender$ or male$ or female$ or man or woman or women or men).tw. (2049175)

65 or/60-64 (2132677)

66 14 and 65 (303)

67 exp Population Groups/ (191780)

68 eh.fs. (112002)

69 (ethnic$ or ethno$ or race$ or racial$).tw. (150638)

70 or/67-69 (333290)

71 10 and 70 (90)

72 14 or 18 or 22 or 28 or 30 or 32 or 36 or 40 or 44 or 51 or 59 or 66 or 71 (1823)

73 limit 72 to english language (1616)

74 animals/ not humans/ (3717557)

75 73 not 74 (1607)

Review Question 3:

Which patient characteristics / criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed GORD to a consultant led medical or surgical service?

Database: Ovid MEDLINE(R) <1946 to July Week 2 2012> (update search conducted on 05 December 2013).

Search Strategy:

---

1 Dyspepsia/ (6821)

2 (dyspep$ or indigestion$).tw. (9703)

3 waterbrash$.tw. (8)

4 (regurg$ not (mitral$ or vascular$ or pulmonar$)).tw. (9577)

5 Heartburn/ (1513)

6 heartburn$.tw. (3370)

7 pyros$.tw. (2949)

8 acid exposure.tw. (1851)

9 exp Esophagitis/ (8912)

10 (esophagit$ or oesophagit$).tw. (10353)

11 exp Gastritis/ (17242)

12 (gastrit$ or gastr$ stas$).tw. (16167)

13 exp Gastroesophageal Reflux/ (20000)

14 exp Duodenogastric Reflux/ (1550)

15 (gord or gerd or ger).tw. (6617)

16 reflux$.tw. (37107)

17 Esophageal Sphincter, Lower/ (510)

18 lower esophageal sphincter.tw. (3226)

19 lower oesophageal sphincter.tw. (901)

20 or/1-19 (92751)

21 Consultants/ (5573)

22 Specialization/ (20669)

23 Gastroenterology/ (7308)

24 (consultant$ or speciali$ or gastroenterolog$ or proctolog$ or expert$).tw. (217588)

25 exp Hospitals/ (186342)

26 exp Hospital Units/ (69860)

27 exp Hospitalization/ (141259)

28 hospital$.tw. (696207)

29 (tertiary-care or secondary-care).tw. (21389)

30 ((tertiary or secondary) adj3 (care or service$ or center$ or centre$ or practice$)).tw. (35460)

31 General Surgery/ (31930)

32 exp Surgical Procedures, Operative/ (2199124)

33 (surg$ or operation$ or operative$).tw. (1380905)

34 Outpatients/ (7494)

35 Outpatient Clinics, Hospital/ (13781)

36 (outpatient$ or out-patient$).tw. (103405)

37 Inpatients/ (10895)

38 (inpatient$ or in-patient$).tw. (996267)

39 or/21-38 (4345444)

40 20 and 39 (46928)

41 exp "Referral and Consultation"/ (52336)

42 (refer or referr$ or consult$ or second opinion$ or gatekeep$).tw. (234511)

43 41 or 42 (259007)

44 40 and 43 (2168)

45 Ambulatory Care/ or ambulatory care facilities/ (44134)

46 Primary Health Care/ (48213)

47 exp General Practice/ (61347)

48 General Practitioners/ (933)

49 Physicians, Family/ (14316)

50 Physicians, Primary Care/ (605)

51 gp$.tw. (97800)

52 ((general or family) adj (practice$ or practitioner$ or physician$ or doctor$)).tw. (72469)

53 primary-care.tw. (57220)

54 ((primary or ambulatory) adj3 (care or health$ or service$ or center$ or centre$ or practice$)).tw. (87434)

55 Community Health Services/ (25377)

56 Community health nursing/ (17833)

57 ((walkin or walk-in or "walk in" or community health) adj3 (care or service$ or centre$ or center$ or clinic$ or facilit$)).tw. (4417)

58 or/45-57 (348834)

59 20 and 43 and 58 (483)

60 44 or 59 (2283)

61 animals/ not humans/ (3663211)

62 60 not 61 (2262)

63 limit 62 to english language (1950)

Review Question 4:

What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease?

Database: Ovid MEDLINE(R) <1946 to September Week 3 2012> (update search conducted by MPC on 06 December 2013)

Search Strategy:

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1 exp Gastroesophageal Reflux/ (20185)

2 exp Duodenogastric Reflux/ (1555)

3 (reflux$ or gord or gerd or ger).tw. (38474)

4 exp Esophagitis/ (8968)

5 (esophagi$ or oesophagi$).tw. (10838)

6 exp Gastritis/ (17333)

7 (gastrit$ or gastr$ stas$).tw. (16290)

8 or/1-7 (71512)

9 Proton Pump Inhibitors/ (2506)

10 Omeprazole/ (8164)

11 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$ or emozul$).tw. (65237)

12 or/9-11 (67160)

13 8 and 12 (6324)

Review Question 5:

In patients with symptoms of dyspepsia who are positive for helicobacter pylori, which eradication regimens are the most clinically effective in the eradication of *H pylori*?

Database: Ovid MEDLINE(R) <1946 to August Week 5 2012> (update search conducted on 02 December 2013)

Search Strategy:

---

1 sequen$.tw. (807727)

2 tripl$.tw. (59536)

3 quadrupl$.tw. (6797)

4 ((standard$ or convention$) adj3 (therap$ or treat$ or regim$)).tw. (75690)

5 or/1-4 (935763)

6 Proton Pump Inhibitors/ (2485)

7 Omeprazole/ (8152)

8 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$).tw. (65001)

9 or/6-8 (66918)

10 exp Nitroimidazoles/ (14617)

11 (nitroimidazole$ or antiprotozoal$ or metronidazole$ or flagyl$ or tinidazole$ or fasigyn$).tw. (13291)

12 Clarithromycin/ (4687)

13 (clarithromycin$ or klaricid$).tw. (5916)

14 exp Amoxicillin/ (8612)

15 (amox$ or amix$ or amoram$ or amoxident$ or alenamox$ or rimoxallin$).tw. (12013)

16 Bismuth/ (4535)

17 (bismuth$ or tripotassium$ or tri-potassium$ or tri potassium$ or de-noltab$ or denoltab$ or de noltab$).tw. (4269)

18 exp Tetracyclines/ (38584)

19 tetracyclin$.tw. (25722)

20 exp Quinolones/ (32885)

21 (quinolon$ or levofloxacin$ or tavinic$ or moxifloxacin$ or avelox$).tw. (13701)

22 or/10-21 (122402)

23 9 and 22 (3088)

24 5 or 23 (937359)

25 exp Helicobacter/ (27735)

26 Helicobacter Infections/ (22948)

27 exp Campylobacter/ (9249)

28 (helicobac$ or campylobact$ or pylori$).tw. (48325)

29 or/25-28 (51267)

30 24 and 29 (7232)

Update search conducted on PubMed on 02 December 2013

Strategy:

Search (#11 or #12)

Search (#9 AND publisher [sb])

Search (#9 AND #10)

Search ("2013/10/10"[Date - Entrez] : "3000"[Date - Entrez])

Search (#7 and #8)

Search (helicobac* or campylobact* or pylori*[Title/Abstract])

Search (#3 or #6)

Search (#4 and #5)

Search (#1 or #2)

Search (nitroimidazole* or antiprotozoal* or metronidazole* or flagyl* or tinidazole* or fasigyn* or clarithromycin* or klaricid* or amox* or amix* or amoram* or amoxident* or alenamox* or rimoxallin* or bismuth* or tripotassium* or tri-potassium* or tri potassium* or de-noltab* or denoltab* or de noltab* or tetracyclin* or quinolon* or levofloxacin* or tavinic* or moxifloxacin* or avelox*[Title/Abstract])

Search (ppi* or proton pump* or omeprazole* or losec* or rabeprazole* or pariet* or pantoprazole* or protium* or lansoprazole* or zoton* or esomeprazole* or nexium*[Title/Abstract])

Search (standard* OR convention* AND therap* OR treat* OR regim*[Title/Abstract])

Search (sequen* or tripl* or quadrupl*[Title/Abstract])

Review Question 6:

What is the effectiveness of laparoscopic fundoplication compared to medical management in patients with GORD?

Database: Ovid MEDLINE(R) <1948 to November Week 3 2011> (update search conducted on 17 December 2013)

Search Strategy:
---

1 exp Gastroesophageal Reflux/ (19796)

2 exp Duodenogastric Reflux/ (1567)

3 (reflux$ or gord or gerd or ger).tw. (37759)

4 Esophageal Sphincter, Lower/ (466)

5 lower esophageal sphincter.tw. (3192)

6 lower oesophageal sphincter.tw. (893)

7 (les or los).tw. (15977)

8 Heartburn/ (1461)

9 heartburn$.tw. (3294)

10 pyros$.tw. (2439)

11 acid exposure.tw. (1801)

12 Dyspepsia/ (6800)

13 (dyspep$ or indigestion$).tw. (9598)

14 (regurg$ or waterbrash$).tw. (23945)

15 exp Esophagitis/ (8866)

16 (esophagi$ or oesophagi$).tw. (10675)

17 exp Gastritis/ (17444)

18 (gastrit$ or gastr$ stas$).tw. (16251)

19 or/1-18 (120456)

20 Fundoplication/ (3123)

21 fundoplicat$.tw. (3941)

22 gastroplicat$.tw. (50)

23 nissen.tw. (2208)

24 (toupet or lind or watson or besley or hill).tw. (15508)

25 (antireflux$ or anti-reflux$ or anti reflux$).tw. (4362)

26 or/20-25 (22949)

27 19 and 26 (6329)

Review Question 7:

What other medical management is effective for patients who do not respond to PPIs, H_2 receptor antagonists, or *H pylori* eradication despite optimum primary care, or patients who have relapsed following surgery?

Database: Ovid MEDLINE(R) <1946 to October Week 4 2012> (update search conducted on 12 December 2013)

Search Strategy:

---

1 exp Gastroesophageal Reflux/ (20261)

2 exp Duodenogastric Reflux/ (1555)

3 (reflux$ or gord or gerd or ger).tw. (38634)

4 Esophageal Sphincter, Lower/ (536)

5 lower esophageal sphincter.tw. (3257)

6 lower oesophageal sphincter.tw. (907)

7 (les or los).tw. (16703)

8 Heartburn/ (1538)

9 heartburn$.tw. (3422)

10 pyros$.tw. (3254)

11 acid exposure.tw. (1885)

12 Dyspepsia/ (6883)

13 (dyspep$ or indigestion$).tw. (9823)

14 (regurg$ or waterbrash$).tw. (24575)

15 exp Esophagitis/ (9004)

16 (esophagi$ or oesophagi$).tw. (10881)

17 exp Gastritis/ (17381)

18 (gastrit$ or gastr$ stas$).tw. (16348)

19 exp Abdominal Pain/ (23831)

20 ((abdom$ or stomach$) adj3 (ache$ or pain$ or discomfort$)).tw. (35707)

21 or/1-20 (172460)

22 Proton Pump Inhibitors/ (2569)

23 Omeprazole/ (8191)

24 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$ or emozul$).tw. (65637)

25 or/22-24 (67572)

26 (nocturn$ or night$ or evening$ or bed$ or sleep$).tw. (246121)

27 ((split$ or separat$ or divi$ or even$ or spread$ or multipl$ or alter$ or chang$ or reduc$ or less$ or small$ or low$) adj3 dos$).tw. (196251)

28 25 and (26 or 27) (2830)

29 21 and 28 (753)

30 exp Histamine H2 Antagonists/ (18029)

31 (h2ra$ or h2-ra$ or "h2 ra$").tw. (413)

32 (histamin$ adj3 (antagon$ or block$ or recep$)).tw. (11117)

33 (h2$ adj3 (antagon$ or hist$ or block$ or recep$)).tw. (14520)

34 cimetidin$.tw. (10207)

35 tagamet.tw. (95)

36 ranitidin$.tw. (5384)

37 zantac.tw. (56)

38 famotidin$.tw. (1635)

39 nizatidin$.tw. (354)

40 axid.tw. (10)

41 or/30-40 (35084)

42 25 and 41 (3913)

43 21 and 42 (1495)

44 Dopamine Antagonists/ (9263)

45 (dopamin$ adj3 (receptor$ or antagonist$)).tw. (27446)

46 prokinetic$.tw. (1882)

47 Metoclopramide/ (4448)

48 (metoclopramide or maxolon).tw. (4925)

49 Domperidone/ (1503)

50 (domperidone or motilium).tw. (1835)

51 (itopride or ganaton).tw. (64)

52 (mosapride or biotonus).tw. (187)

53 or/44-52 (38965)

54 21 and 53 (1474)

55 exp Laparoscopy/ (62058)

56 laparoscopes/ (3291)

57 surgical procedures, Minimally Invasive/ (15264)

58 (laparoscop$ or celioscop$ or keyhole$).tw. (72639)

59 or/55-58 (95003)

60 Fundoplication/ (3277)

61 fundoplicat$.tw. (4067)

62 gastroplicat$.tw. (48)

63 nissen.tw. (2247)

64 (toupet or lind or watson or besley or hill).tw. (15936)

65 (antireflux$ or anti-reflux$ or anti reflux$).tw. (4397)

66 or/60-65 (23538)

67 59 and 66 (2960)

68 21 and 67 (2290)

69 29 or 43 or 54 or 68 (5510)

Review Question 8:

Should surveillance be used for patients with Barrett's Oesophagus to detect progression to cancer, and improve survival?

Database: Ovid MEDLINE(R) <1946 to May Week 4 2012> (update search conducted on 18 December 2013)

Search Strategy:

---

1 Barrett Esophagus/ (5504)

2 barrett$.tw. (6461)

3 ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4142)

4 ((metaplas$ or dysplasi$ or neoplasi$) adj3 (column$ or intestin$ or epithel$ or oesophag$ or esophag$ or mucos$ or high-grade$ or low-grade$)).tw. (13822)

5 or/1-4 (21574)

6 exp Mass Screening/ (90868)

7 exp Population Surveillance/ (44090)

8 (screen$ or surveillan$ or monitor$).tw. (843147)

9 or/6-8 (896405)

10 exp Endoscopy/ (231412)

11 endoscop$.tw. (116970)

12 chromoendoscop$.tw. (489)

13 (esophagoscop$ or oesophagoscop$).tw. (1731)

14 exp Biopsy/ (205812)

15 biops$.tw. (251781)

16 or/10-15 (604770)

17 9 and 16 (43493)

18 5 and 17 (2222)

Broad update search for all review questions (apart from RQ5) conducted on PubMed on 11 December 2013

Strategy:

Search (#21 or #23)

Search (#19 and #20)

Search (#19 and #22)

Search ("2013/12/09"[Date - Entrez] : "3000"[Date - Entrez])

Search publisher[sb]

Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)

Search ((metaplas* or dysplasi* or neoplasi*[Title/Abstract])) AND (epithel* or oesophag* or esophag* or mucos*[Title/Abstract])

Search ((column* or speciali* or intestinali*[Title/Abstract])) AND (epithel* or oesophag* or esophag* or mucos*[Title/Abstract])

Search (((((reflux*[Title/Abstract]) NOT (coronar* or heart* or mitral* or vascular* or pulmonar* or vesico* or uter* or laryn*[Title/Abstract]))))

Search lower esophageal sphincter[Title/Abstract]

Search lower oesophageal sphincter[Title/Abstract]

Search pyros*[Title/Abstract]

Search acid exposure[Title/Abstract]

Search esophagit*[Title/Abstract]

Search oesophagit*[Title/Abstract]

Search gord[Title/Abstract]

Search gerd[Title/Abstract]

Search ger[Title/Abstract]

Search indigestion*[Title/Abstract]

Search barrett*[Title/Abstract]

Search heartburn[Title/Abstract]

Search (((acid*[Title/Abstract]) AND regurg*[Title/Abstract]))

Search dyspep*[Title/Abstract]

Search waterbrash*[Title/Abstract]

6.2.2.2 Study design filters

The MEDLINE systematic reviews and RCT search filters that were used where required for some of the review questions above are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Specific systematic reviews filter

Appended to review questions 4 and 7

1 Meta-Analysis.pt. (37837)

2 Meta-Analysis as Topic/ (12594)

3 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (45065)

4 (systematic$ adj4 (review$ or overview$)).tw. (40425)

5 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3110)

6 ((studies or trial$) adj1 (review$ or overview$)).tw. (6557)

7 (integrat$ adj2 (research or review$ or literature)).tw. (3111)

8 (pool$ adj1 (analy$ or data)).tw. (7682)

9 (handsearch$ or (hand adj2 search$)).tw. (4484)

10 (manual$ adj2 search$).tw. (2443)

11 or/1-10 (105950)

Broad systematic reviews filter

Appended to review questions 5 and 6

1 Meta-Analysis.pt. (37837)

2 Meta-Analysis as Topic/ (12594)

3 Review.pt. (1757173)

4 exp Review Literature as Topic/ (6618)

5 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (45065)

6 (review$ or overview$).ti. (240634)

7 (systematic$ adj4 (review$ or overview$)).tw. (40425)

8 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3110)

9 ((studies or trial$) adj1 (review$ or overview$)).tw. (6557)

10 (integrat$ adj2 (research or review$ or literature)).tw. (3111)

11 (pool$ adj1 (analy$ or data)).tw. (7682)

12 (handsearch$ or (hand adj2 search$)).tw. (4484)

13 (manual$ adj2 search$).tw. (2443)

14 or/1-13 (1894766)

Specific RCT filter

Appended to review questions 4 and 7

1 Randomized Controlled Trial.pt. (342057)
2 Controlled Clinical Trial.pt. (85675)
3 Placebos/ (31568)
4 Random Allocation/ (76571)
5 Double-Blind Method/ (118432)
6 Single-Blind Method/ (17072)
7 Cross-Over Studies/ (30968)
8 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (569547)
9 (random$ adj2 allocat$).tw. (18127)
10 placebo$.tw. (141042)
11 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (116052)
12 (crossover$ or (cross adj over$)).tw. (52321)
13 or/1-12 (945299)

Broad RCT filter

Appended to review questions 5 and 6

1 Randomized Controlled Trial.pt. (342057)
2 Controlled Clinical Trial.pt. (85675)
3 Clinical Trial.pt. (476279)
4 exp Clinical Trials as Topic/ (264246)
5 Placebos/ (31568)
6 Random Allocation/ (76571)
7 Double-Blind Method/ (118432)
8 Single-Blind Method/ (17072)
9 Cross-Over Studies/ (30968)
10 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (569547)
11 (random$ adj2 allocat$).tw. (18127)
12 placebo$.tw. (141042)
13 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (116052)

14 (crossover$ or (cross adj over$)).tw. (52321)

15 or/1-14 (1198484)

16 animals/ not humans/ (3718637)

17 15 not 16 (1120965)

4.2.3 Economic evaluations and quality of life data

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley)
- Health Economic Evaluations Database – HEED (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Health economics studies on dyspepsia and GORD

The searches were undertaken in March 2012. The specific economic evaluations filter was appended to the following search strategy to identify relevant evidence.

Database: Ovid MEDLINE(R) <1946 to February Week 4 2012>

Search Strategy:

---

1 Dyspepsia/ (6726)

2 (dyspep$ or indigestion$).tw. (9523)

3 (regurg$ or waterbrash$).tw. (23471)

4 Heartburn/ (1468)

5 heartburn$.tw. (3288)

6 pyros$.tw. (2421)

7 acid exposure.tw. (1804)

8 exp Peptic Ulcer/ (70434)

9 ((peptic$ or gastr$ or duoden$ or stomach$) adj3 ulcer$).tw. (50958)

10 exp Esophagitis/ (8754)

11 (esophagi$ or oesophagi$).tw. (10524)

12 exp Gastritis/ (17049)

13 (gastrit$ or gastr$ stas$).tw. (15913)

14 exp Gastroesophageal Reflux/ (19636)

15 exp Duodenogastric Reflux/ (1533)

16 (reflux$ or gord or gerd or ger).tw. (37306)

17 Esophageal Sphincter, Lower/ (467)

18 lower esophageal sphincter.tw. (3160)

19 lower oesophageal sphincter.tw. (892)

20 (les or los).tw. (15672)

21 or/1-20 (183837)

22 exp Gastrointestinal Neoplasms/ (251799)

23 ((stomach$ or oesoph$ or esoph$ or intestin$ or gastric$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (82446)

24 ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (1286)

25 or/22-24 (264951)

26 21 or 25 (428356)

Health economics studies for Barrett's oesophagus

The searches were undertaken in June 2012. The specific economic evaluations filter was appended to the following search strategy to identify relevant evidence.

Database: Ovid MEDLINE(R) <1946 to May Week 5 2012>

Search Strategy:

---

1 Barrett Esophagus/ (5527)

2 barrett$.tw. (6488)

3 ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4149)

4 ((metaplas$ or dysplasi$ or neoplasi$) adj3 (column$ or intestin$ or epithel$ or oesophag$ or esophag$ or mucos$ or high-grade$ or low-grade$)).tw. (13859)

5 or/1-4 (21633)

Health economics studies on RQ1 Diagnostic utility of non-urgent endoscopy in patients with signs and symptoms of dyspepsia or GORD

The searches were undertaken in June 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

Database: Ovid MEDLINE(R) <1946 to May Week 4 2013>

Search Strategy:

---

1 exp Gastroesophageal Reflux/ (21073)
2 exp Duodenogastric Reflux/ (1566)
3 (reflux$ or gord or gerd or ger).tw. (39865)
4 Esophageal Sphincter, Lower/ (589)
5 lower esophageal sphincter.tw. (3312)
6 lower oesophageal sphincter.tw. (912)
7 (les or los).tw. (17474)
8 pyros$.tw. (3852)
9 acid exposure.tw. (1990)
10 Dyspepsia/ (7033)
11 (dyspep$ or indigestion$).tw. (10122)
12 (regurg$ or waterbrash$).tw. (25208)
13 hypergastrin*.tw. (1550)
14 Heartburn/ (1650)
15 heartburn$.tw. (3667)
16 exp Abdominal Pain/ (24439)
17 ((abdom$ or stomach$) adj3 (ache$ or pain$ or discomfort$)).tw. (36738)
18 Chest Pain/ (8747)
19 ((chest$ or thora$) adj3 (ache$ or pain$ or discomfort$)).tw. (24330)
20 (epigastri$ adj3 (ache$ or pain$ or discomfort$)).tw. (3388)
21 or/1-20 (179880)
22 exp Endoscopy, Digestive System/ (78532)
23 (endoscop$ or gastroscop$ or videoscop$).tw. (127383)
24 chromoendoscop$.tw. (533)
25 (esophagoscop$ or oesophagoscop$).tw. (1764)
26 or/22-25 (163419)
27 21 and 26 (19172)
28 risk factors/ (525551)
29 risk$.tw. (1128239)
30 "Signs and Symptoms"/ (422)
31 (sign* adj symptom*).tw. (3508)
32 or/28-31 (1322964)

33 27 and 32 (2645)

34 exp Hernia/ (59410)

35 (hernia$ or enterocele$).tw. (48852)

36 34 or 35 (72210)

37 27 and 36 (1248)

38 Eructation/ (281)

39 (eructat$ or belch$ or burp$).tw. (998)

40 38 or 39 (1111)

41 27 and 40 (126)

42 Polymorphism, Single Nucleotide/ (57063)

43 single nucleotide polymorphism.tw. (12199)

44 or/42-43 (59882)

45 27 and 44 (11)

46 ((paediatric or pediatric) adj reflux$).tw. (9)

47 27 and 46 (1)

48 (famil* adj history).tw. (38382)

49 27 and 48 (137)

50 ((gastro-oesophageal$ or gastrooesophageal$ or gastroesophageal$ or gastro-esophageal$) adj junction$).tw. (1937)

51 27 and 50 (332)

52 exp Diet/ (183353)

53 (diet$ or food$ or nutrition$).tw. (636973)

54 52 or 53 (700671)

55 27 and 54 (1154)

56 exp Smoking/ (115460)

57 (smok$ or cigarette$ or cigar$ or tobacco$).tw. (201772)

58 56 or 57 (229102)

59 27 and 58 (484)

60 exp Drinking Behavior/ (54157)

61 (alcohol$ or drink$).tw. (260642)

62 or/60-61 (272215)

63 27 and 62 (559)

64 body mass index/ (72497)

65 (body mass index$ or bmi$ or quetelet$ index$).tw. (110696)

66 Body Weight/ (156912)

67 exp Overweight/ (131550)

68 (weight$ or overweight$ or obes$ or body fat).tw. (729928)

69 or/64-68 (888634)

70 27 and 69 (1677)

71 Age Factors/ (358917)

72 Aging/ (180659)

73 Geriatrics/ (26153)

74 exp Aged/ (2217442)

75 Middle Aged/ (3152892)

76 (age$ or aging or elder$ or geriatric$ or old$).tw. (2851598)

77 or/71-76 (5547763)

78 33 and 77 (1955)

79 Sex/ (7200)

80 Sex Factors/ (202863)

81 Men/ (2537)

82 Women/ (13211)

83 (sex or sexes or gender$ or male$ or female$ or man or woman or women or men).tw. (2096355)

84 or/79-83 (2180475)

85 33 and 84 (886)

86 exp Population Groups/ (197734)

87 eh.fs. (115535)

88 (ethnic$ or ethno$ or race$ or racial$).tw. (155957)

89 or/86-88 (343593)

90 27 and 89 (280)

Health economics questions on Q2: Symptoms indicating endoscopy for Barrett's oesophagus plus economic evaluations filter

The searches were undertaken in January 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

Database: Ovid MEDLINE(R) <1946 to November Week 3 2012>

Search Strategy:

---

1 Barrett Esophagus/ (5721)

2 barrett$.tw. (6728)

3 ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4248)

4 or/1-3 (10773)

5 exp Endoscopy/ (239333)

6 (endoscop$ or gastroscop$ or videoscop$).tw. (124226)

7 chromoendoscop$.tw. (520)

8 (esophagoscop$ or oesophagoscop$).tw. (1759)

9 or/5-8 (288290)

10 4 and 9 (3859)

11 risk factors/ (509982)

12 risk$.tw. (1089808)

13 or/11-12 (1277173)

14 10 and 13 (1162)

15 exp Hernia/ (58796)

16 (hernia$ or enterocele$).tw. (47965)

17 15 or 16 (71313)

18 10 and 17 (365)

19 Eructation/ (277)

20 (eructat$ or belch$ or burp$).tw. (971)

21 19 or 20 (1080)

22 10 and 21 (12)

23 Chest Pain/ (8528)

24 ((chest or thora$) adj3 (pain$ or ache$ or discomfort$)).tw. (23962)

25 Heartburn/ (1546)

26 (heartburn$ or pyros$).tw. (6758)

27 or/23-26 (33479)

28 10 and 27 (308)

29 bile$ reflux$.tw. (683)

30 10 and 29 (40)

31 ((gastro-oesophageal$ or gastrooesophageal$ or gastroesophageal$ or gastro-esophageal$) adj junction$).tw. (1885)

32 10 and 31 (182)

33 exp Diet/ (178778)

34 (diet$ or food$ or nutrition$).tw. (620250)

35 33 or 34 (683111)

36 10 and 35 (78)

37 exp Smoking/ (113467)

38 (smok$ or cigarette$ or cigar$ or tobacco$).tw. (197375)

39 37 or 38 (224382)

40 10 and 39 (117)

41 exp Drinking Behavior/ (53104)

42 (alcohol$ or drink$).tw. (255464)

43 or/41-42 (266912)

44 10 and 43 (100)

45 body mass index/ (69416)

46 (body mass index$ or bmi$ or quetelet$ index$).tw. (105683)

47 Body Weight/ (155399)

48 exp Overweight/ (127702)

49 (weight$ or overweight$ or obes$ or body fat).tw. (711690)

50 or/45-49 (866901)

51 10 and 50 (184)

52 Age Factors/ (353807)

53 Aging/ (178208)

54 Geriatrics/ (26028)

55 exp Aged/ (2180488)

56 Middle Aged/ (3100516)

57 (age$ or aging or elder$ or geriatric$ or old$).tw. (2786610)

58 or/52-57 (5449058)

59 14 and 58 (688)

60 Sex/ (7245)

61 Sex Factors/ (199058)

62 Men/ (2519)

63 Women/ (13153)

64 (sex or sexes or gender$ or male$ or female$ or man or woman or women or men).tw. (2053611)

65 or/60-64 (2137179)

66 14 and 65 (303)

67 exp Population Groups/ (192157)

68 eh.fs. (112208)

69 (ethnic$ or ethno$ or race$ or racial$).tw. (150987)

70 or/67-69 (333935)

71 10 and 70 (90)

Economic searches on Review Question 3: Dyspepsia – referral to consultancy led services

The searches were undertaken in June 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

Database: Ovid MEDLINE(R) <1946 to June Week 1 2013>

Search Strategy:

---

1 Dyspepsia/ (7104)

2 (dyspep$ or indigestion$).tw. (10283)

3 waterbrash$.tw. (9)

4 (regurg$ not (mitral$ or vascular$ or pulmonar$)).tw. (10180)

5 Heartburn/ (1675)

6 heartburn$.tw. (3729)

7 pyros$.tw. (4408)

8 acid exposure.tw. (2064)

9 exp Esophagitis/ (9438)

10 (esophagit$ or oesophagit$).tw. (11129)

11 exp Gastritis/ (17784)

12 (gastrit$ or gastr$ stas$).tw. (16950)

13 exp Gastroesophageal Reflux/ (21360)

14 exp Duodenogastric Reflux/ (1575)

15 (gord or gerd or ger).tw. (7359)

16 reflux$.tw. (39318)

17 exp Peptic Ulcer/ (72084)

18 ((peptic* or marginal* or gastroduodenal* or curling*) adj1 ulcer*).tw. (24585)

19 Esophageal Sphincter, Lower/ (609)

20 lower esophageal sphincter.tw. (3349)

21 lower oesophageal sphincter.tw. (917)

22 or/1-21 (161641)

23 Consultants/ (5634)

24 Specialization/ (21087)

25 Gastroenterology/ (7659)

26 (consultant$ or speciali$ or gastroenterolog$ or proctolog$ or expert$).tw. (241395)

27 exp Hospitals/ (194688)

28 exp Hospital Units/ (74766)

29 exp Hospitalization/ (151911)

30 hospital$.tw. (744975)

31 (tertiary-care or secondary-care).tw. (24034)

32 ((tertiary or secondary) adj3 (care or service$ or center$ or centre$ or practice$)).tw. (39887)

33 General Surgery/ (32747)

34 exp Surgical Procedures, Operative/ (2314506)

35 (surg$ or operation$ or operative$).tw. (1462215)

36 Outpatients/ (8472)

37 Outpatient Clinics, Hospital/ (14128)

38 (outpatient$ or out-patient$).tw. (111536)

39 Inpatients/ (12079)

40 (inpatient$ or in-patient$).tw. (1081478)

41 or/23-40 (4606154)

42 22 and 41 (76731)

43 exp "Referral and Consultation"/ (54863)

44 (refer or referr$ or consult$ or second opinion$ or gatekeep$).tw. (254611)

45 43 or 44 (279750)

46 42 and 45 (2627)

47 Ambulatory Care/ or ambulatory care facilities/ (46189)

48 Primary Health Care/ (52103)

49 exp General Practice/ (62966)

50 General Practitioners/ (1558)

51 Physicians, Family/ (14791)

52 Physicians, Primary Care/ (963)

53 gp$.tw. (107669)

54 ((general or family) adj (practice$ or practitioner$ or physician$ or doctor$)).tw. (76526)

55 primary-care.tw. (63248)

56 ((primary or ambulatory) adj3 (care or health$ or service$ or center$ or centre$ or practice$)).tw. (95956)

57 Community Health Services/ (26382)

58 Community health nursing/ (18097)

59 ((walkin or walk-in or "walk in" or community health) adj3 (care or service$ or centre$ or center$ or clinic$ or facilit$)).tw. (4810)

60 or/47-59 (372571)

61 22 and 45 and 60 (543)

62 46 or 61 (2755)

Health economics studies on RQ 4 clinical effectiveness of PPIs in patients with severe erosive reflux disease

The searches were undertaken in May 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

Database: Ovid MEDLINE(R) <1946 to May Week 1 2013>

Search Strategy:

---

1 exp Gastroesophageal Reflux/ (21027)

2 exp Duodenogastric Reflux/ (1565)

3 (reflux$ or gord or gerd or ger).tw. (39779)

4 exp Esophagitis/ (9302)

5 (esophagi$ or oesophagi$).tw. (11290)

6 exp Gastritis/ (17631)

7 (gastrit$ or gastr$ stas$).tw. (16681)

8 or/1-7 (73538)

9 Proton Pump Inhibitors/ (3052)

10 Omeprazole/ (8882)

11 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$ or emozul$).tw. (68843)

Health economics studies on RQ 5 *H pylori*

The searches were undertaken in November 2011 and updated in Feb 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

1 sequen$.tw. (780022)

2 tripl$.tw. (57062)

3 quadrupl$.tw. (6508)

4 ((standard$ or convention$) adj3 (therap$ or treat$ or regim$)).tw. (72267)

5 or/1-4 (902378)

6 Proton Pump Inhibitors/ (2108)

7 Omeprazole/ (8195)

8 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$).tw. (63366)

9 or/6-8 (65253)

10 exp Nitroimidazoles/ (14387)

11 (nitroimidazole$ or antiprotozoal$ or metronidazole$ or flagyl$ or tinidazole$ or fasigyn$).tw. (12981)

12 Clarithromycin/ (4696)

13 (clarithromycin$ or klaricid$).tw. (5782)

14 exp Amoxicillin/ (8484)

15 (amox$ or amix$ or amoram$ or amoxident$ or alenamox$ or rimoxallin$).tw. (11714)

16 Bismuth/ (4343)

17 (bismuth$ or tripotassium$ or tri-potassium$ or tri potassium$ or de-noltab$ or denoltab$ or de noltab$).tw. (4148)

18 exp Tetracyclines/ (38179)

19 tetracyclin$.tw. (25264)

20 exp Quinolones/ (31777)

21 (quinolon$ or levofloxacin$ or tavinic$ or moxifloxacin$ or avelox$).tw. (13087)

22 or/10-21 (119449)

23 9 and 22 (3112)

24 5 or 23 (904002)

25 exp Helicobacter/ (27822)

26 Helicobacter Infections/ (23064)

27 exp Campylobacter/ (9027)

28 (helicobac$ or campylobact$ or pylori$).tw. (47975)

29 or/25-28 (50973)

30 24 and 29 (7159)

Health economics searches on review Question 6 - Effectiveness of laparoscopic fundoplication compared to medical management in patients with GORD

The searches were undertaken in November 2011. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

Database: Ovid MEDLINE(R) <1948 to November Week 3 2011>

---

1 exp Gastroesophageal Reflux/ (19796)

2 exp Duodenogastric Reflux/ (1567)

3 (reflux$ or gord or gerd or ger).tw. (37759)

4 Esophageal Sphincter, Lower/ (466)

5 lower esophageal sphincter.tw. (3192)

6 lower oesophageal sphincter.tw. (893)

7 (les or los).tw. (15977)

8 Heartburn/ (1461)

9 heartburn$.tw. (3294)

10 pyros$.tw. (2439)

11 acid exposure.tw. (1801)

12 Dyspepsia/ (6800)

13 (dyspep$ or indigestion$).tw. (9598)

14 (regurg$ or waterbrash$).tw. (23945)

15 exp Esophagitis/ (8866)

16 (esophagi$ or oesophagi$).tw. (10675)

17 exp Gastritis/ (17444)

18 (gastrit$ or gastr$ stas$).tw. (16251)

19 or/1-18 (120456)

20 Fundoplication/ (3123)

21 fundoplicat$.tw. (3941)

22 gastroplicat$.tw. (50)

23 nissen.tw. (2208)

24 (toupet or lind or watson or besley or hill).tw. (15508)

25 (antireflux$ or anti-reflux$ or anti reflux$).tw. (4362)

26 or/20-25 (22949)

27 19 and 26 (6329)

Health economics searches on review Question 7 – other medical or surgical treatments for GORD/dyspepsia

The searches were undertaken in July 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence

Database: Ovid MEDLINE(R) <1946 to June Week 4 2013>

Search Strategy:

---

1 exp Gastroesophageal Reflux/ (21834)

2 exp Duodenogastric Reflux/ (1598)

3 (reflux$ or gord or gerd or ger).tw. (41116)

4 Esophageal Sphincter, Lower/ (636)

5 lower esophageal sphincter.tw. (3396)

6 lower oesophageal sphincter.tw. (951)

7 (les or los).tw. (18554)

8 Heartburn/ (1711)

9 heartburn$.tw. (3837)

10 pyros$.tw. (4848)

11 acid exposure.tw. (2136)

12 Dyspepsia/ (7239)

13 (dyspep$ or indigestion$).tw. (10520)

14 (regurg$ or waterbrash$).tw. (25940)

15 exp Esophagitis/ (9626)

16 (esophagi$ or oesophagi$).tw. (11821)

17 exp Gastritis/ (18039)

18 (gastrit$ or gastr$ stas$).tw. (17309)

19 exp Abdominal Pain/ (25169)

20 ((abdom$ or stomach$) adj3 (ache$ or pain$ or discomfort$)).tw. (38261)

21 or/1-20 (184907)

22 Proton Pump Inhibitors/ (3452)

23 Omeprazole/ (9602)

24 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$ or emozul$).tw. (73807)

25 or/22-24 (75976)

26 (nocturn$ or night$ or evening$ or bed$ or sleep$).tw. (265507)

27 ((split$ or separat$ or divi$ or even$ or spread$ or multipl$ or alter$ or chang$ or reduc$ or less$ or small$ or low$) adj3 dos$).tw. (212809)

28 25 and (26 or 27) (3312)

29 21 and 28 (952)

30 exp Histamine H2 Antagonists/ (18438)

31 (h2ra$ or h2-ra$ or "h2 ra$").tw. (456)

32 (histamin$ adj3 (antagon$ or block$ or recep$)).tw. (11644)

33 (h2$ adj3 (antagon$ or hist$ or block$ or recep$)).tw. (15499)

34 cimetidin$.tw. (10324)

35 tagamet.tw. (97)

36 ranitidin$.tw. (5605)

37 zantac.tw. (58)

38 famotidin$.tw. (1728)

39 nizatidin$.tw. (375)

40 axid.tw. (11)

41 or/30-40 (36871)

42 25 and 41 (4294)

43 21 and 42 (1658)

44 Dopamine Antagonists/ (9777)

45 (dopamin$ adj3 (receptor$ or antagonist$)).tw. (29089)

46 prokinetic$.tw. (2029)

47 Metoclopramide/ (4516)

48 (metoclopramide or maxolon).tw. (5018)

49 Domperidone/ (1556)

50 (domperidone or motilium).tw. (1883)

51 (itopride or ganaton).tw. (73)

52 (mosapride or biotonus).tw. (211)

53 or/44-52 (41139)

54 21 and 53 (1541)

55 exp Laparoscopy/ (66357)

56 laparoscopes/ (3399)

57 surgical procedures, Minimally Invasive/ (16403)

58 (laparoscop$ or celioscop$ or keyhole$).tw. (77671)

59 or/55-58 (101549)

60 Fundoplication/ (3485)

61 fundoplicat$.tw. (4270)

62 gastroplicat$.tw. (51)

63 nissen.tw. (2360)

64 (toupet or lind or watson or besley or hill).tw. (17231)

65 (antireflux$ or anti-reflux$ or anti reflux$).tw. (4603)

66 or/60-65 (25195)

67 59 and 66 (3160)

68 21 and 67 (2451)

69 29 or 43 or 54 or 68 (6046)

Health economics studies for RQ8 on Barrett's oesophagus surveillance

The searches were undertaken in June 2012. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence.

Database: Ovid MEDLINE(R) <1946 to June Week 3 2012>

Search Strategy:

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1 Barrett Esophagus/ (5540)

2 barrett$.tw. (6502)

3 ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4150)

4 ((metaplas$ or dysplasi$ or neoplasi$) adj3 (column$ or intestin$ or epithel$ or oesophag$ or esophag$ or mucos$ or high-grade$ or low-grade$)).tw. (13889)

5 or/1-4 (21677)

6 exp Mass Screening/ (91380)

7 exp Population Surveillance/ (44528)

8 (screen$ or surveillan$ or monitor$).tw. (850390)

9 or/6-8 (903995)

10 exp Endoscopy/ (232503)

11 endoscop$.tw. (117555)

12 chromoendoscop$.tw. (493)

13 (esophagoscop$ or oesophagoscop$).tw. (1734)

14 exp Biopsy/ (206772)

15 biops$.tw. (253125)

16 or/10-15 (607756)

17 9 and 16 (43821)

18 5 and 17 (2236)

Health economics update search

A broad update search was conducted in November and December 2013.

Database: Ovid MEDLINE(R) <1946 to November Week 3 2013>

Search Strategy:

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1 Dyspepsia/ (7350)

2 (dyspep$ or indigestion$).tw. (10747)

3 (regurg$ or waterbrash$).tw. (26570)

4 Heartburn/ (1741)

5 heartburn$.tw. (3927)

6 pyros$.tw. (5409)

7 acid exposure.tw. (2187)

8 exp Peptic Ulcer/ (72959)

9 ((peptic$ or gastr$ or duoden$ or stomach$) adj3 ulcer$).tw. (53892)

10 exp Esophagitis/ (9796)

11 (esophagi$ or oesophagi$).tw. (12055)

12 exp Gastritis/ (18238)

13 (gastrit$ or gastr$ stas$).tw. (17592)

14 exp Gastroesophageal Reflux/ (22243)

15 exp Duodenogastric Reflux/ (1603)

16 (reflux$ or gord or gerd or ger).tw. (41924)

17 Esophageal Sphincter, Lower/ (671)

18 lower esophageal sphincter.tw. (3442)

19 lower oesophageal sphincter.tw. (960)

20 (les or los).tw. (19218)

21 or/1-20 (204562)

22 exp Gastrointestinal Neoplasms/ (290193)

23 ((stomach$ or oesoph$ or esoph$ or intestin$ or gastric$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (95901)

24 ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (1544)

25 or/22-24 (305698)

26 21 or 25 (487765)

27 "Value of Life"/ (5495)

28 Quality-Adjusted Life Years/ (7347)

29 quality adjusted life.tw. (6165)

30 (qaly$ or qald$ or qale$ or qtime$).tw. (5151)

31 disability adjusted life.tw. (1204)

32 daly$.tw. (1179)

33 Health Status Indicators/ (21035)

34 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15680)

35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1085)

36 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2653)

37 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20)

38 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (334)

39 (euroqol or euro qol or eq5d or eq 5d).tw. (3796)

40 (hye or hyes).tw. (53)

41 health$ year$ equivalent$.tw. (37)

42 (health adj3 state adj3 utilit$).tw. (335)

43 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (5348)

44 (hui or hui1 or hui2 or hui3).tw. (884)

45 disutili$.tw. (214)

46 rosser.tw. (73)

47 quality of wellbeing.tw. (6)

48 quality of well-being.tw. (353)

49 qwb.tw. (173)

50 willingness to pay.tw. (2162)

51 standard gamble$.tw. (673)

52 time trade off.tw. (741)

53 time tradeoff.tw. (212)

54 tto.tw. (585)

55 (preferen$ weight$ or health state preferen$).tw. (257)

56 or/27-55 (62401)

57 26 and 56 (1701)

58 limit 57 to english language (1615)

59 limit 58 to ed=20120201-20131204 (277)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 03, 2013>

Search Strategy:

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1 Dyspepsia/ (0)

2 (dyspep$ or indigestion$).tw. (702)

3 (regurg$ or waterbrash$).tw. (1426)

4 Heartburn/ (0)

5 heartburn$.tw. (208)

6 pyros$.tw. (731)

7 acid exposure.tw. (100)

8 exp Peptic Ulcer/ (0)

9 ((peptic$ or gastr$ or duoden$ or stomach$) adj3 ulcer$).tw. (2009)

10 exp Esophagitis/ (0)

11 (esophagi$ or oesophagi$).tw. (588)

12 exp Gastritis/ (0)

13 (gastrit$ or gastr$ stas$).tw. (665)

14 exp Gastroesophageal Reflux/ (0)

15 exp Duodenogastric Reflux/ (0)

16 (reflux$ or gord or gerd or ger).tw. (2733)

17 Esophageal Sphincter, Lower/ (0)

18 lower esophageal sphincter.tw. (129)

19 lower oesophageal sphincter.tw. (17)

20 (les or los).tw. (1831)

21 or/1-20 (9799)

22 exp Gastrointestinal Neoplasms/ (2)

23 ((stomach$ or oesoph$ or esoph$ or intestin$ or gastric$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (5670)

24 ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (103)

25 or/22-24 (5726)

26 21 or 25 (14913)

27 "Value of Life"/ (0)

28 Quality-Adjusted Life Years/ (0)

29 quality adjusted life.tw. (574)

30 (qaly$ or qald$ or qale$ or qtime$).tw. (469)

31 disability adjusted life.tw. (153)

32 daly$.tw. (140)

33 Health Status Indicators/ (0)

34 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (1204)

35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (373)

36 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (305)

37 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (3)

38 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (11)

39 (euroqol or euro qol or eq5d or eq 5d).tw. (449)

40 (hye or hyes).tw. (2)

41 health$ year$ equivalent$.tw. (2)

42 (health adj3 state adj3 utilit$).tw. (41)

43 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (450)

44 (hui or hui1 or hui2 or hui3).tw. (82)

45 disutili$.tw. (22)

46 rosser.tw. (1)

47 quality of wellbeing.tw. (2)

48 quality of well-being.tw. (9)

49 qwb.tw. (5)

50 willingness to pay.tw. (234)

51 standard gamble$.tw. (31)

52 time trade off.tw. (57)

53 time tradeoff.tw. (7)

54 tto.tw. (55)

55 (preferen$ weight$ or health state preferen$).tw. (23)

56 or/27-55 (3571)

57 26 and 56 (64)

58 limit 57 to english language (60)

Database: Embase <1980 to 2013 Week 48>

Search Strategy:

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1 dyspepsia/ (24578)

2 (dyspep$ or indigestion$).tw. (15222)

3 indigestion/ (1623)

4 (regurg$ or waterbrash$).tw. (37061)

5 heartburn/ (9009)

6 heartburn$.tw. (5633)

7 pyros$.tw. (7133)

8 acid exposure.tw. (2969)

9 exp peptic ulcer/ (99843)

10 ((peptic$ or gastr$ or duoden$ or stomach$) adj3 ulcer$).tw. (63195)

11 exp esophagitis/ (23422)

12 (esophagi$ or oesophagi$).tw. (17107)

13 exp gastritis/ (50481)

14 (gastrit$ or gastr$ stas$).tw. (22739)

15 exp gastroesophageal reflux/ (43044)

16 exp duodenogastric reflux/ (2508)

17 laryngopharyngeal reflux/ (814)

18 (reflux$ or gord or gerd or ger).tw. (59125)

19 lower esophagus sphincter/ (9546)

20 lower esophageal sphincter.tw. (4406)

21 lower oesophageal sphincter.tw. (1121)

22 (les or los).tw. (40231)

23 or/1-22 (333773)

24 gastrointestinal tumor/ (9980)

25 exp stomach cancer/ (63618)

26 exp esophagus cancer/ (37040)

27 exp intestine cancer/ (158216)

28 ((stomach$ or oesoph$ or esoph$ or intestin$ or gastric$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (124439)

29 ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (2091)

30 or/24-29 (300340)

31 23 or 30 (605636)

32 Quality Adjusted Life Year/ (11654)

33 Short Form 36/ (10749)

34 Health Status/ (82773)

35 quality adjusted life.tw. (8411)

36 (qaly$ or qald$ or qale$ or qtime$).tw. (8313)

37 disability adjusted life.tw. (1479)

38 daly$.tw. (1569)

39 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (22104)

40 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1435)

41 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3905)

42 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (34)

43 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (320)

44 (euroqol or euro qol or eq5d or eq 5d).tw. (6317)

45 (hye or hyes).tw. (84)

46 health$ year$ equivalent$.tw. (43)

47 (health adj3 state adj3 utilit$).tw. (542)

48 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (7535)

49 (hui or hui1 or hui2 or hui3).tw. (1206)

50 disutili$.tw. (351)

51 rosser.tw. (88)

52 quality of wellbeing.tw. (19)

53 quality of well-being.tw. (372)

54 qwb.tw. (192)

55 willingness to pay.tw. (3188)

56 standard gamble$.tw. (770)

57 time trade off.tw. (978)

58 time tradeoff.tw. (224)

59 tto.tw. (846)

60 (preferen$ weight$ or health state preferen$).tw. (371)

61 or/32-60 (133769)

62 31 and 61 (3878)

63 limit 62 to embase (3493)

64 limit 63 to (conference abstract or conference paper) (758)

65 63 not 64 (2735)

66 limit 65 to english language (2606)

67 limit 66 to em=201201-201348 (522)

Database: Cochrane Library

Search Name: ICG - Dyspepsia - Health Economics - Update Search 04 Dec 2013

Date Run: 04/12/13 09:55:25.811

Description: 04 Dec 2013

ID	SearchHits
#1	MeSH descriptor: [Dyspepsia] this term only 867
#2	dyspep* or indigestion*:ti,ab,kw 2360
#3	regurg* or waterbrash*:ti,ab,kw 875
#4	MeSH descriptor: [Heartburn] this term only 267
#5	heartburn*:ti,ab,kw 982
#6	pyros*:ti,ab,kw 93
#7	acid exposure*:ti,ab,kw 1355
#8	MeSH descriptor: [Peptic Ulcer] explode all trees 3601
#9	(peptic* or gastr* or duoden* or stomach*) near ulcer*:ti,ab,kw 6634
#10	MeSH descriptor: [Esophagitis] explode all trees 608
#11	esophagi* or oesophagi*:ti,ab,kw 1356
#12	MeSH descriptor: [Gastritis] explode all trees 514
#13	gastrit* or gastr* stas*:ti,ab,kw 1355
#14	MeSH descriptor: [Gastroesophageal Reflux] explode all trees 1387
#15	MeSH descriptor: [Duodenogastric Reflux] explode all trees 52
#16	reflux* or gord or gerd or ger:ti,ab,kw 3438
#17	MeSH descriptor: [Esophageal Sphincter, Lower] this term only 35

#18 lower esophageal sphincter:ti,ab,kw 504

#19 lower oesophageal sphincter:ti,ab,kw 504

#20 les or los:ti,ab,kw 2050

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 16791

#22 MeSH descriptor: [Gastrointestinal Neoplasms] explode all trees 7424

#23 (stomach* or oesoph* or esoph* or intestin* or gastric*) near (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or malign*):ti,ab,kw 4435

#24 (upper digestive* or upper gastr* or upper gi) near (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or malign*):ti,ab,kw 115

#25 #22 or #23 or #24 9400

#26 #21 or #25 from 2012 to 2013 1078

PubMed Search

#7	Search (#5 and #6)	178
#8	Search publisher [sb]	444846
#6	Search ("2013/12/02"[Date - Publication] : "3000"[Date - Publication])	13997
#5	Search (#1 or #4)	427055
#4	Search (#2 and #3)	67921
#1	Search (dyspep* or indigestion or regurg* or waterbrash or heartburn or pyros* or â€œacid exposureâ€• or esophagi* or oesophagi* or gastrit* or gastr* or stas* or reflux* or gord or gerd or ger or â€œlower esophageal sphincterâ€• or les or los[Title/Abstract])	402629
#3	Search ulcer*[Title/Abstract]	157670
#2	Search (peptic* or gastr* or duoden* or stomach[Title/Abstract])	380100

HEED

1 dyspep* or indigestion* or regurg* or waterbrash or heartburn or pyros* or gastrit* or acid* or gastr* or stas* or reflux* or gord or gerd or ger or les or los

AND

2 qaly* or qald* or qale* or qtime* or quality or valu* or weight* or scor* or measure

Notes:

PubMed – only limited by date, adding the publisher limit retrieved too many results (not necessarily recent).

HEED – Line 1: Exported new articles (2012 – 2013). Lines 1 AND 2: exported records from 2012 – 2013

Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Specific economic evaluations filter

1 "Value of Life"/ (5218)

2 Quality-Adjusted Life Years/ (5682)

3 quality adjusted life.tw. (4551)

4 (qaly$ or qald$ or qale$ or qtime$).tw. (3807)

5 disability adjusted life.tw. (870)

6 daly$.tw. (882)

7 Health Status Indicators/ (17920)

8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (12459)

9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (898)

10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (1936)

11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (18)

12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (308)

13 (euroqol or euro qol or eq5d or eq 5d).tw. (2690)

14 (hye or hyes).tw. (52)

15 health$ year$ equivalent$.tw. (36)

16 (health adj3 state adj3 utilit$).tw. (232)

17 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (4170)

18 (hui or hui1 or hui2 or hui3).tw. (698)

19 disutili$.tw. (168)

20 rosser.tw. (72)

21 quality of wellbeing.tw. (5)

22 quality of well-being.tw. (297)

23 qwb.tw. (150)

24 willingness to pay.tw. (1659)

25 standard gamble$.tw. (578)

26 time trade off.tw. (600)

27 time tradeoff.tw. (190)

28 tto.tw. (456)

29 (preferen$ weight$ or health state preferen$).tw. (209)

30 Or/1-29

Economic evaluations

1 Economics/

2 exp "Costs and Cost Analysis"/

3 Economics, Dental/

4 exp Economics, Hospital/

5 exp Economics, Medical/

6 Economics, Nursing/

7 Economics, Pharmaceutical/

8 Budgets/

9 exp Models, Economic/

10 Markov Chains/

11 Monte Carlo Method/

12 Decision Trees/

13 econom$.tw.

14 cba.tw.

15 cea.tw.

16 cua.tw.

17 markov$.tw.

18 (monte adj carlo).tw.

19 (decision adj2 (tree$ or analys$)).tw.

20 (cost or costs or costing$ or costly or costed).tw.

21 (price$ or pricing$).tw.

22 budget$.tw.

23 expenditure$.tw.

24 (value adj2 (money or monetary)).tw.

25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.

26 or/1-25

Quality of life

1 "Value of Life"/

2 Quality-Adjusted Life Years/

3 quality adjusted life.tw.

4 (qaly$ or qald$ or qale$ or qtime$).tw.

5 disability adjusted life.tw.

6 daly$.tw.

7 Health Status Indicators/

8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

13 (euroqol or euro qol or eq5d or eq 5d).tw.

14 (hye or hyes).tw.

15 health$ year$ equivalent$.tw.

16 (health adj3 state adj3 utilit$).tw.

17 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw.

18 (hui or hui1 or hui2 or hui3).tw.

19 disutili$.tw.

20 rosser.tw.

21 quality of wellbeing.tw.

22 quality of well-being.tw.

23 qwb.tw.

24 willingness to pay.tw.

25 standard gamble$.tw.

26 time trade off.tw.

27 time tradeoff.tw.

28 tto.tw.

29 (preferen$ weight$ or health state preferen$).tw.

30 or/1-30

C.3 Summary of the modified GRADE approach

For the review questions [2014 update]:

Review question 1: When should (and with what indications) patients with uninvestigated dyspepsia be referred for endoscopy for further investigation and review of treatment plan?

Review question 2: Which risk factors indicate endoscopy in order to exclude Barrett's oesophagus?

Review question 3: Which patient characteristics/clinical indicators/criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed GORD managed in primary care to a consultant led medical or surgical service (specialist services)?

For the above three review questions [2014 update], a modified-GRADE approach was used for critical appraisal and evidence synthesis to aid decision making. The criteria used in the modified-GRADE approach were adapted from the Hayden et al. (2006) QUIPS checklist for prognostic study (link for the Guideline Manual 2012).

The methodology of the modified-GRADE approach was as follow:

Quality appraisal using modified-GRADE approach

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a common, sensible and transparent approach to grading quality of evidence which was developed by experts internationally. Over 70 international guidance developing organisations have endorsed the use of GRADE, including NICE, SIGN, NHS Quality Improvement Scotland, Cochrane Collaboration, WHO, BMJ Clinical Evidence, Agency for Healthcare Research and Quality (AHRQ) and many others.

GRADE was originally developed for grading quality of intervention and diagnostic accuracy study only. However, for the purpose of this particular review question on risk factors, the GRADE criteria were modified and adapted by using the Hayden et al. (2006) checklist for prognostic study (NICE Guideline Manual, 2012). The modified-GRADE criteria were used to appraise the quality of individual studies, as well as the quality of individual risk factors across different studies. The rationales for downgrading the evidence based on the five modified-GRADE criteria were explicitly reported using 'footnote' for each modified-GRADE profile.

Summary of the modified-GRADE approach:

Section 1: Outcome vs individual study, and meta-analysis

In GRADE approach for intervention question, the quality of evidence on each outcome is assessed according to the impact of the risk of bias from the study to that particular outcome. If there is more than one study that reported such outcome, the overall judgement of the quality for that outcome across different studies will be made.

This is because in the same intervention study (e.g. RCT), there may be different levels or magnitude of the impact of the risk of bias on different outcomes measured in the same study. For example, in a single-blinded RCT (assessor-blinded only) on antibiotics for infected wound, the risk of bias for patient-reported pain of the wound (outcome 1) would be different compared to bacteria eradication rate (based on histology) (outcome 2) due to the single-blinded design of the study.

In prognostic study (or clinical prediction model), these varying degrees of risk of bias in a study do not apply same as in an intervention study. This is because in a multivariate regression model (MRM), the sources of the risk of bias commonly came from how the data of the individual risk factors or predictors was collected as a whole in a study, and what kinds of adjustment were made in the MRM regarding baseline confounders and covariates. Hence, the risk of bias in a study would have impacted the MRM as whole (i.e. all risk factors or predictors entered in the MRM equally). Therefore, the quality of an individual study would apply across to all risk factors or predictors in that particular individual study.

Due to the varying methods used in different studies (e.g. different multivariate regression models in different studies used different dependent variables as risk factors or predictors, used different covariates, adjusted for different confounding factors), in other words, there are no two exactly identical multivariate regression models that could be pooled in its entirety. The only approach to conduct meta-analysis is to obtain IPD data from each study and then re-run a single MRM using all the IPD data from all included studies. This would be outside the development timeframe of this guideline.

Therefore, no meta-analysis was conducted to combine individual risk factors or predictors across different MRMs in different studies. Nevertheless, if there are more than one included studies for a particular risk factor or predictor, the evidence would be presented based on individual risk factors or predictors across different studies to aid discussion and decision making. Otherwise, the evidence would be presented as individual studies.

Section 2: Criteria and downgrading

There are four quality categories in GRADE, namely 'High', 'Moderate', 'Low' and 'Very low'. For prognostic study (or clinical prediction model), case control or cross-sectional study was considered as appropriate study designs and hence under the modified-GRADE approach, these two study designs would start from 'High' quality (or high 'confidence' in the effect estimates). Then the evidence would be downgraded based on the following modified framework:

GRADE criteria	Hayden (2006) QUIPS criteria, plus other statistical rules	Downgrading
Risk of bias	1) Prospective study. 2) Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.* Note*: To adjust potential confounders that are not	Downgrade 1 level if either (1) or (2) or both were not satisfied If there are more than one included studies,

	part of the independent variables (risk factors) being studied.	downgrade 1 level if either (1) or (2) or both were not satisfied in >50% of the included studies.
Indirectness	1) The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. 2) The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. 3) The outcome of interest is adequately measured in study participants, sufficient to limit potential bias.	i) Downgrade 1 level if either (1) or (2) or (3) were not satisfied. ii) Downgrade 2 levels if more than 2 criteria were not satisfied. If there are more than one included studies, downgrade 1 level if >50% of the included studies been downgraded due to i). If there are more than one included studies, downgrade 2 levels if >50% of the included studies been downgraded due to ii).
Inconsistency	1) Same direction of effect estimates across all different studies. 2) Overlaps of 95%CI.	Downgrade 1 level if either (1) or (2) or both were not satisfied. Note: this criterion is not applicable to single study.
Imprecision	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results (i.e. multivariate analysis - logistic regression model): 1) Model diagnostics: Assumption of normality (1a); Multicollinearity (1b); Goodness-of-fit (1c). 2) Reproducibility (validation) .	i) Downgrade 1 level if either (1) or (2) was not satisfied. ii) Downgrade 2 levels if both (1) and (2) were not satisfied. If there are more than one included studies, downgrade 2 levels if >50% of the included studies been downgraded due to i) or ii).
Other considerations	1) Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias.	Downgrade 1 level if (1) was not satisfied. If there are more than one included studies, downgrade 1 level if >50% of the included studies been downgraded.

For the quality appraisal for individual studies for review question 2, please see below. For the full modified-GRADE profiles, please also see appendix F.

[Note: For review question 1, since only 2 studies were included and hence the 2 individual studies were discussed in the Full guideline chapter; for review question 3, no study identified that met the inclusion criteria].

Table below shows review question 2: Quality appraisal of individual studies – Modified GRADE – Criteria adapted from the Hayden et al (2006) checklist.

	•*Prospective (1)* •Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. (2)* Note*: To adjust potential confounders that are not part of the independent variables (risk factors) being studied.	•The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. (1) •The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. (2) •The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. (3)	•*Same direction of effect estimates across different studies. (1)* •*Overlaps of 95%CI (2)*	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results (i.e. multivariate analysis - logistic regression model): •*Model diagnostics: Assumption of normality (1a); Multicollinearity (1b); Goodness-of-fit (1c).* •*Reproducibility (validation) (2)*	•Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. (1)	
	Risk of bias (Study design limitations)	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Overall quality**
Abrams (2008)	(1): NO, (2): unable to adjust obesity, GORD, H.pylori	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Ford (2005)	(1): NO, (2): unable to adjust BMI, smoking, alcohol	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Johansson (2007)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Voutilainen (2000)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Jonaitis (2011)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Omer (2012)	(1): NO, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Lam (2008)	(1): NO, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Menon (2011)	(1): NO, (2): unable to adjust BMI, GORD, H.pylori, etc.	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Thrift (2012)**	(1): NO, (2): Unclear	All Yes	N/A for single study	(1b-1c): YES, (2): YES	YES	Moderate
Khoury (2012)	(1): NO, (2): unable to adjust age, H.pylori, etc.	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Nelsen (2012)	(1): YES, (2): Some adjusted for BMI but not others	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Low
Rubenstein (2010)	(1): NO, (2): YES = adj age, gender, indication	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Bu (2006)	(1): YES, (2): YES = adj age & gender	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Low
Conio (2002)	(1): YES, (2): YES = adj centre, gender, age	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Low
Fan (2009)	(1): NO, (2): YES = adj GORD symptoms	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Thrift (2003)	(1): NO, (2): YES = adj age, sex, smoking, alcohol	All Yes	N/A for single study	(1a-1c): NO, (2): NO	Yes	Very low
Campos (2001)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Eloubeidi (2001)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Gerson (2001)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Gerson (2007)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Koek (2008)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Lieberman (1997)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Wang (2008)	(1): NO, (2): controlled for potential confounding var	All Yes	N/A for single study	(1b-1c): YES, (2): NO	YES	Low
De Mas (1999)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Nandurkar (1997)	(1): YES, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Dietz (2006)	(1): YES, (2): Unclear	(1): NO = only included >40 yrs, (2-3): YES	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Gatenby (2008)	(1): NO, (2): Unclear	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Romero (2002)	(1): YES, (2): YES = adj age, gender, obesity, etc.	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Low
Thompson (2009)	(1): YES, (2): YES = adj gender, age, ethnicity, BMI, etc.	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Low
Jacobson (2011)	(1): NO, (2): YES = adj GORD, age, BMI, alcohol, etc.	(1): NO = only female nurses	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Stein (2005)	(1): NO, (2): unable to adjust confounders for weight	(1): NO = only male	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low
Dickman (2005)	(1): YES, (2): unable to adjust GORD symptoms, etc.	All Yes	N/A for single study	(1a-1c): NO, (2): NO	YES	Very low