

1 Appendix C: Review protocols, searches 2 and summary of modified GRADE [update 3 2014]

C.1 Review protocols

5 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. (note: uninvestigated dyspepsia defined as those who have not had endoscopy before or those who have not had endoscopy within last 12 months)
Language	English only.
Study design	No restriction but exclude case series, case reports and qualitative studies.
Status	Published papers (full text only).
Population	<p><u>Include</u></p> <ul style="list-style-type: none"> • Dyspepsia • Functional dyspepsia • GORD symptoms • Heartburn • Chest pain • Epigastric pain • Upper abdominal pain • Reflux • Hypergastrinaemia • Ulcer • persistent symptoms <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Patients <18 years • Endoscopically confirmed GORD, Ulcer dyspepsia, or confirmed functional dyspepsia at baseline <p>Previous endoscopy within 12 months.</p>
Intervention/ indications	<p><u>Include</u></p> <p>For 'endoscopy'</p> <ul style="list-style-type: none"> • 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

Exclude

- Endosonography/ultrasound
- Capsule endoscopy.

Control	<ul style="list-style-type: none"> • No endoscopy • Delayed endoscopy
Outcomes	<ul style="list-style-type: none"> • Health 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	<p><u>Include</u></p> <ul style="list-style-type: none"> • Patients with newly onset signs/symptoms • Primary care setting or patients referred to secondary care for endoscopy <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 background studies	<p>Edenholm M et al (1985). Endoscopic findings in patients with ulcer-like dyspepsia. Scand J Gastroenterol Suppl. 1985;109:163-7</p> <p>Rabeneck L, Wristers K, Soucek J, et al (2003). Impact of upper endoscopy on satisfaction in patients with previously uninvestigated dyspepsia. Gastrointest Endosc 2003;57:295-9</p> <p>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.</p>

6 **Table 2: Review question 2**

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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	No restriction but exclude case series, case reports and qualitative studies.
Status	Published papers (full text only).
Population	<p>Adults (18 years and older)</p> <p><u>Include</u></p> <ul style="list-style-type: none"> • Histological confirmed Barrett's oesophagus • Metaplasia/specialised intestinal metaplasia • Dysplasia (high and low grade) • Columnar epithelium <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<p><u>Include</u></p> <ul style="list-style-type: none"> • 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'

	<ul style="list-style-type: none">• Previous / Paediatric reflux surgery <p><u>Exclude</u></p> <ul style="list-style-type: none">• 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	<ul style="list-style-type: none"> • Proportion with positive diagnosis of Barrett's oesophagus • Size/length of Barrett's oesophagus.
Other criteria for inclusion/exclusion of studies	<p><u>Include</u></p> <ul style="list-style-type: none"> • Studies that report outcomes in multivariate analysis • Prospective studies <p>(Note: Due to the limited volume of prospective studies, the GDG later agreed to drop down the hierarchy of evidence and to include retrospective studies as well).</p> <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 background studies	<p>Kuo CJ (2010). Frequency and risk factors for Barrett's esophagus in Taiwanese patients: a prospective study in a tertiary referral center. <i>Digestive Diseases & Sciences</i>. 55(5):1337-43, 2010</p> <p>Xiong LS (2010). Prevalence and risk factors of Barrett's esophagus in patients undergoing endoscopy for upper gastrointestinal symptoms. <i>Journal of Digestive Diseases</i>. 11(2):83-7, 2010</p> <p>Anderson LA (2007). Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. <i>World J Gastroenterol</i>. 2007 Mar 14;13(10):1585-94</p> <p>Stein DJ (2005). The association of body mass index with Barrett's oesophagus. <i>Aliment Pharmacol Ther</i>. 2005 Nov 15;22(10):1005-10</p> <p>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. <i>Gastroenterology</i>. 2009 136:799-805.</p> <p>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.</p>

	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	<p>Adults (18 years and older)</p> <p><u>Include*</u></p> <ul style="list-style-type: none"> • GORD/GERD • Dyspepsia (investigated/uninvestigated dyspepsia, non-ulcer dyspepsia, functional dyspepsia) • Peptic ulcer disease • Heartburn • Reflux <p>(*populations covered – based on CG17 plus functional dyspepsia)</p> <p>PLUS other search terms</p> <ul style="list-style-type: none"> • 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 <i>H pylori</i> test and treat.
Intervention/indications	<p><u>Include (search terms)</u></p> <ul style="list-style-type: none"> • Specialist • Consultant • Gastroenterologist

	<ul style="list-style-type: none">• Upper GI surgery• Complications• Refractory• Escalate• Referral• Expert• Secondary• Tertiary• Hospital• Outpatient• Investigations <p><u>Exclude</u></p> <ul style="list-style-type: none">• Primary care• GP• Endoscopy.
Control	N/A

Outcomes	<p><u>Critical</u></p> <ul style="list-style-type: none"> • Health related QOL • Resolution/improvement of Symptoms / VAS • Patient satisfaction <p><u>Important</u></p> <ul style="list-style-type: none"> • Medication use/dose • GP/Hospital visits • Heartburn (% of days free). •
Other criteria for inclusion/exclusion of studies	<p><u>Include</u></p> <ul style="list-style-type: none"> • Any study illustrates 'who' (patient characteristic, clinical indicators, criteria) should be managed outside primary care that resulted in better patient outcomes. <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Studies where the healthcare structure is considerably different to the UK where upwards referral for specialist treatment is not comparable. •
Search strategies	<p>No restriction on study design (but will exclude case series, case reports, narrative review and qualitative study).</p>
Review strategies	<ul style="list-style-type: none"> • 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 background studies	<p><u>Systematic reviews</u> None indentified</p> <p><u>Studies</u></p> <p>van Bommel MJJ (2001). Consultations and referrals for dyspepsia in general practice—a one year database survey. <i>Postgrad Med J</i> 2001;77:514-518</p> <p>Jones RH (1993). Problems with implementing guidelines: a randomised controlled trial of consensus management of dyspepsia. <i>Qual Health Care</i> 1993;2:217-221</p> <p>Flameling RD (2010). Different characteristics of patients with gastro-oesophageal reflux disease on their path through healthcare: a population follow-up study. <i>European Journal of Gastroenterology & Hepatology</i> May 2010 - Volume 22 - Issue 5 - pp 578-582</p> <p>Gerson LB (2011). Development of a refractory gastro-oesophageal reflux score using an administrative claims database. <i>Alimentary Pharmacology & Therapeutics</i> 34(5):555-67, 2011 Sep.</p>

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> <ul style="list-style-type: none"> Los Angeles classification grade C or D, Savary-Miller grade 3 or 4 <u>Exclude</u> <ul style="list-style-type: none"> Los Angeles classification grade A 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> <ul style="list-style-type: none"> Omeprazole Rabeprazole (sodium) Lansoprazole Esomeprazole Pantoprazole <u>Exclude</u> <ul style="list-style-type: none"> Dexlansoprazole – not licensed in UK H₂RAs (exclude from decision data set, but possibly use in comparison dataset in network analysis).
Control	<ul style="list-style-type: none"> Placebo H₂RA Existing self-care (Each of the interventions listed in interventions box above will be

	compared to one another also).
Outcomes	<ul style="list-style-type: none"> • Endoscopic appearance/change 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	<p><u>Include</u></p> <ul style="list-style-type: none"> • Studies comparing the above listed treatment regimens • >30-days follow-up period <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 background studies	<p><u>Systematic reviews</u></p> <p>Edwards SJ et al (2006). Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis – a comparison of esomeprazole and other PPIs. <i>Alimentary Pharmacology & Therapeutics</i> 2006 24: 743-750</p>

	<p>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</p> <p><u>RCTs (some included in reviews above)</u></p> <p>Fennerty MB, Johanson JF, Hwang C, et al (2005). Efficacy of esomeprazole 40mg versus lansoprazole 30mg for healing moderate to severe erosive esophagitis. <i>Aliment Pharmacol Ther</i> 2005; 21: 455–63</p> <p>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. <i>Dig Dis Sci</i>. 2006 May;51(5):844-50</p> <p>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. <i>Dig Dis Sci</i>. 2006 May;51(5):852-7.</p>
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9 **Table 5: Review question 5i**

	Details	Additional comments
Review question	In patients with symptoms of dyspepsia who are positive for <i>Helicobacter pylori</i> , which eradication regimens are the most clinically effective in the eradication of <i>H pylori</i> ?	
Objectives	To compare different regimens to see which is the most effective in the eradication of <i>H pylori</i> .	
Language	English only.	
Study design	Systematic reviews/meta-analysis, RCTs (blind or open-label).	
Status	Published papers (full text only).	
Population	<p>Adults (18 years and older) who have the following:</p> <ul style="list-style-type: none"> • Symptoms of dyspepsia • Positive test for <i>H pylori</i> • Naïve to previous antibiotic treatment <p><u>Include</u></p> <ul style="list-style-type: none"> • Uninvestigated dyspepsia • Ulcer dyspepsia (gastric or peptic) • Functional/non ulcer dyspepsia <p>Can consider together for analysis – same risk associated with failure</p> <p><u>Exclude</u></p>	<p>All subgroups (uninvestigated dyspepsia, ulcer dyspepsia, and functional dyspepsia) to be considered together.</p> <p>It may be possible to perform subgroup analysis on gastric and peptic ulcer separately if data allows</p> <p>Subgroup analysis will be performed, if possible, on intolerance</p>

	<ul style="list-style-type: none"> • Studies with patients with <i>H pylori</i> infection being treated for diagnosis other than dyspepsia - gastric cancer, NSAID related GI irritation, or population screening. • Studies where <i>H pylori</i> 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. 	to penicillin
Intervention/indications	<p>Comparison of the effectiveness of the following interventions – all compared to each other</p> <p>A) SEQUENTIAL THERAPY B) TRIPLE THERAPY C) QUADRUPLE THERAPY WITH BISMUTH D) QUARDUPLE THERAPY WITH THREE ANTIBIOTICS</p> <p>We will include 'Individual/named antibiotics' in two classes (Penicillins and Macrolides) but assume a class effect in all others</p> <p><u>Include</u></p> <ul style="list-style-type: none"> • Studies comparing different lengths of the above listed regimens • Follow up period to be a minimum of one month after treatment <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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. 	<p>Interventions listed here have been suggested to be the most relevant</p> <p>The search will be based on the regimen/type used and for each names drug included</p> <p>Assume all PPIs are equally effective when used within regimen for H Pylori eradication</p> <p>License status of antibiotics for dyspepsia (one or more named drug per class is licensed for this indication)</p> <ul style="list-style-type: none"> • Macrolides ✓ • Quinolones (off label) • Penicillins ✓ • Nitroimidazole ✓ • Tetracyclines ✓ indicated for GI infection • Rifamycin (off label)
Control	<ul style="list-style-type: none"> • 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	<p><u>Critical</u></p> <ul style="list-style-type: none"> • Eradication rate • Adherence to medication <p><u>Important</u></p> <ul style="list-style-type: none"> • 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	<p><u>Include</u></p> <ul style="list-style-type: none"> • Studies with mixed populations (i.e. patients who have and have not tested positive for <i>H pylori</i>) will only be included if outcomes are clearly separated between these groups. <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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). 	<p>We have assumed that:</p> <ul style="list-style-type: none"> • single or dual therapies are not used • while some macrolide antibiotics other than clarithromycin are reported in the literature, they are not used in the UK • <i>H. pylori</i> eradication regimes using H2RAs are no longer used
Search strategies	Systematic reviews/meta-analysis, RCTs, quasi-RCTs.	
Review strategies	<p>The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies</p> <p>Data on all included studies will be extracted into evidence tables</p> <p>Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis)</p>	

	<p>All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements</p> <p>Sub group analyses will be undertaken for the underlying cause of dyspepsia where appropriate.</p>	
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Identified key background studies	<p><u>Systematic reviews</u></p> <ul style="list-style-type: none">• 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 <p><u>RCTs (some included in reviews above)</u></p> <ul style="list-style-type: none">• 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	
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	<ul style="list-style-type: none"> • Vaira D, Zullo A, Vakil N, et al (2008). Sequential therapy versus standard triple-drug therapy for <i>Helicobacter pylori</i> eradication: a randomized trial. <i>Ann Intern Med</i> 2007;146:556–63 • Wu DC, Hsu PI, Wu JY, et al (2008). Randomized controlled comparison of sequential and quadruple (concomitant) therapies for <i>H pylori</i> infection. <i>Gastroenterology</i> 2008;134:137. 	
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10 **Table 6: Review question 5ii**

	Details	Additional comments
Review question	What <i>H pylori</i> 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 <i>H pylori</i> 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	<p>Adults (18 years and older) who have the following:</p> <ul style="list-style-type: none"> • Symptoms of dyspepsia • Positive test for <i>H pylori</i> • Failed the first line eradication regimen recommended in Q5i <p><u>Include</u></p> <ul style="list-style-type: none"> • Uninvestigated dyspepsia • Ulcer dyspepsia (gastric or peptic) • Functional/non ulcer dyspepsia <p>Can consider together for analysis – same risk associated with failure</p> <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Studies with patients with <i>H pylori</i> infection being treated for diagnosis other than dyspepsia - gastric cancer, NSAID related GI irritation, or population screening. • Studies where <i>H pylori</i> has not been confirmed (i.e. studies in high prevalence areas where infection is assumed) • Endoscopically confirmed GORD 	<p>All subgroups (uninvestigated dyspepsia, ulcer dyspepsia, and functional dyspepsia) to be considered together.</p> <p>It may be possible to perform subgroup analysis on gastric and peptic ulcer separately if data allows.</p> <p>Subgroup analysis will be performed, if possible, on intolerance to penicillin.</p>

	<ul style="list-style-type: none"> • Studies where 2nd line treatment was commenced within one month following completion of 1st line treatment. 	
Intervention/indications	<p>Comparison of the effectiveness of the following interventions – all compared to each other</p> <p>SEQUENTIAL THERAPY</p> <p>TRIPLE THERAPY</p> <ul style="list-style-type: none"> • Ab x 2 + PPI • Ab x 1 + PPI + Bis • Ab x 2 + H2RA • Ab x 1 + H2RA + Bis <p>QUADRUPLE THERAPY WITH BISMUTH</p> <ul style="list-style-type: none"> • Ab x 3 + Bis • Ab x 2 + PPI + Bis • Ab x 2 + H2RA + Bis <p>QUARDUPLE THERAPY WITH THREE ANTIBIOTICS</p> <ul style="list-style-type: none"> • Ab x 3 + PPI • Ab x 3 + H2RA <p>We will include ‘Individual/named antibiotics’ in two classes (Penicillins and Macrolides) but assume a class effect in all others</p> <p><u>Include</u></p> <ul style="list-style-type: none"> • Studies comparing different lengths of the above listed regimens • Follow up period to be a minimum of one month after treatment <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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). 	<p>Assume all PPIs are equally effective when used within regimen for H Pylori eradication.</p>
Control	<p><u>Include</u></p> <ul style="list-style-type: none"> • SEQUENTIAL THERAPY • MONOTHERAPY <ul style="list-style-type: none"> ○ Ab alone ○ PPI alone 	

	<ul style="list-style-type: none">○ H2RA alone● DUAL THERAPY<ul style="list-style-type: none">○ Ab x 2○ Ab x 1 + PPI○ Ab x 1 + H2RA● TRIPLE THERAPY<ul style="list-style-type: none">○ Ab x 3○ Ab x 2 + H2RA○ Ab x 1 + H2RA + Bis● QUADRUPLE THERAPIES<ul style="list-style-type: none">○ Ab x 4○ Ab x 3 + H2RA○ Ab x 3 + Bis○ Ab x 2 + H2RA + Bis <p>Sequential / Triple / Quad therapy with off-label antibiotic included</p> <p>Each of the interventions will be compared to one another.</p>	
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Outcomes	<p><u>Critical</u></p> <ul style="list-style-type: none"> • Eradication rate • Adverse events <p><u>Important</u></p> <ul style="list-style-type: none"> • Effect on symptoms • Adherence to medication • Recurrence rate • Eradication by resistance status. 	
Other criteria for inclusion/exclusion of studies	<p><u>Include</u></p> <ul style="list-style-type: none"> • Studies with mixed populations (i.e. patients who have and have not tested positive for <i>H pylori</i>) will only be included if outcomes are clearly separated between these groups • Studies using off-label drugs in all arms for 2nd line <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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. 	<p>We have assumed that:</p> <ul style="list-style-type: none"> • single or dual therapies are not used • while some macrolide antibiotics other than clarithromycin are reported in the literature, they are not used in the UK.
Search strategies	Systematic reviews/meta-analysis, RCTs.	
Review strategies	<ul style="list-style-type: none"> • The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of 	

	<p>individual studies</p> <ul style="list-style-type: none"> • 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 background studies	<p><u>Systematic reviews</u></p> <ul style="list-style-type: none"> • 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. <p><u>RCTs</u></p> <ul style="list-style-type: none"> • 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 question 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	<ul style="list-style-type: none"> • GORD/GERD/REFLUX

	<ul style="list-style-type: none"> • Heartburn • Acid exposure/indigestion • Waterbrash • Oesophagitis • With positive test for reflux (pH monitoring/manometry/ doscopy) <p><u>Include</u></p> <ul style="list-style-type: none"> • Patients with symptoms >1year • Patients with stable symptoms for >3months (without change in medication) • Patients with symptoms expected to continue for 2 years <p>Subgroup/sensitivity analysis Treatment naïve patients (if data are available)</p> <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Patients <18 years • Previous Surgery for GORD, or oesophogastirc surgery • Patients with GORD and high grade dysplasia.
<p>Intervention/ indications</p>	<p><u>Include</u></p> <ul style="list-style-type: none"> • Laparoscopic Fundoplication (either total/full , partial, or floppy) • Nissen • Anti reflux surgery <p>Subgroup/sensitivity analysis Total/full fundoplication vs other techniques (if data are available)</p> <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Open (Nissen) fundoplication • Endoscopic ablative procedures • Other minimally invasive surgical procedures.
<p>Control</p>	<p><u>Include</u></p> <ul style="list-style-type: none"> • Medical therapy with PPIs as at least one element of treatment • Esopmenprazole • Lamsoprazole • Omeprazole • Pantoprazole • Raberazole Sodium <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Studies with H₂RAs (histamine receptor agonists) only (monotherapy) • Antacids • Other surgery.

Outcomes	<ul style="list-style-type: none"> • 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	<p><u>Include</u></p> <ul style="list-style-type: none"> • Robotic Laparoscopic – but treat same as ‘human’ laparoscopic (Interventional Procedures programme has concluded that these are in effect the same class of intervention) <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 background studies	<p><u>Systematic reviews</u></p> <p>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</p> <p>Catarci M (2004). Evidence-based appraisal of antireflux fundoplication. Annals of Surgery 239 (3) 325-337.2004</p> <p>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</p> <p>Markar SR(2010). Robotic vs laparoscopic Nissen fundoplication for gastro-</p>

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

Studies

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 <i>H pylori</i> 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	<p><u>Include</u></p> <ul style="list-style-type: none"> • GORD / GERD / REFLUX • Heartburn • Acid exposure • Oesophagitis • Dyspepsia • Upper abdominal pain <p>AND/PLUS</p> <ul style="list-style-type: none"> • On 40mg dose PPI bd/ H2RA • Patients with symptoms for >1 month • Refractory • Treatment failure • Relapse • Symptomatic • Specialist • Secondary care • Consultant • Hospital • Secondary care <p><u>Exclude</u></p> <p>Patients <18 years H2RA or PPI or <i>H pylori</i> eradication treatment naïve patients.</p>
Intervention/ indications	<p><u>Include</u></p> <ul style="list-style-type: none"> • Split dose PPI • Nocturnal dose PPI • Dual/combination therapy PPI plus H2RA treatment • Prokinetics/dopamine receptor antagonists (metoclopramide, domperidone, itopride, mosapride) • Laparoscopic (Nissen) fundoplication <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<u>Include</u> <ul style="list-style-type: none">• Standard pharmacological interventions• No intervention• Self treatment.

Outcomes	<p><u>Critical</u></p> <ul style="list-style-type: none"> • Health related QOL • Heartburn (% days free) • Remission of symptoms (dichotomous outcome) <p><u>Important</u></p> <ul style="list-style-type: none"> • Acid reflux – 24 hr pH monitoring (% time <4) • Mortality • Adverse events (specific to each sub-question).
Other criteria for inclusion/exclusion of studies	<p><u>Include</u></p> <ul style="list-style-type: none"> • UK or Developed world setting • Crossover trials <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Studies with follow up <6 months • Allocation by patient preference • Allocation by case selection.
Search strategies	<p>RCTs, Quasi RCTs, systematic reviews, observational studies, cohort studies, case control studies.</p>
Review strategies	<ul style="list-style-type: none"> • 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 background studies	<p><u>Systematic reviews</u></p> <p>Pan T, Wang Y, Guo Z, Wang Q (2004). Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough</p> <p><u>Studies (these may be included within the systematic reviews listed above)</u></p> <p>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</p> <p>Khoury RM, Katz PO, Hammod R, Castell DO (1999). Bedtime ranitidine does</p>

	<p>not eliminate the need for a second daily dose of omeprazole to suppress nocturnal gastric pH. <i>Alimentary Pharmacology and Therapeutics</i> 1999; 13(5):675-678</p> <p>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. <i>Alimentary Pharmacology & Therapeutics</i> 23(5), 649-653.</p>
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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	<p><u>Include</u></p> <ul style="list-style-type: none"> • 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 <p>Minimum length of time since diagnosis with Barrett's 6 months</p> <p><u>Exclude</u></p> <ul style="list-style-type: none"> • Patients <18 years • Previous Surgery for GORD or oesophogastirc surgery. • Previous surveillance programme • Alarm signs for referral • Other stratified patient cohort. • Carcinoma

	<ul style="list-style-type: none"> • Studies that do not provide endoscopic criteria for definition of BO.
Intervention/ indications	<p><u>Include</u></p> <ul style="list-style-type: none"> • Biopsy • Quadrant/circumferential • Surveillance • Monitoring • Endoscopy AND gastrointestinal • Repeat screening/mass screening • Protocol/programme <p><u>Exclude</u></p> <ul style="list-style-type: none"> • 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	<p><u>Include</u></p> <p>Endoscopy as needed Spontaneous detection Incidental identification Ad hoc endoscopy No surveillance.</p>

Outcomes	<ul style="list-style-type: none"> • 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 adenocarcinoma and stage identified • GP visits.
Other criteria for inclusion/exclusion of studies	<p><u>Include</u> 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 dysplasia or cancer (resection oesophagectomy, or ablative endoscopic techniques)</p> <p><u>Exclude</u> Studies with follow up <3 years Studies with n<100.</p>
Search strategies	<p>RCTs, Quasi RCTs, systematic reviews, Non-randomised comparative studies, historically controlled studies (before and after), case control studies, cohort studies, case-series.</p>
Review strategies	<ul style="list-style-type: none"> • 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 background studies	<p><u>Systematic reviews</u> NON RCT Jankowski JA (2002). Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. Gastroenterology. 122(2):588-90.</p> <p><u>Studies</u> NON RCT MacDonald CE (2000). Final results from 10 year cohort of patients undergoing</p>

	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.

10.2 IS search strategies

10.2.1 Scoping searches

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

19

Guidelines/website	Systematic review/economic evaluations
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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

2.2 Main searches

21 Sources searched for the guideline

- 22 • Cochrane Database of Systematic Reviews – CDSR (Wiley)
- 23 • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- 24 • Database of Abstracts of Reviews of Effects – DARE (Wiley)
- 25 • Health Technology Assessment Database – HTA (Wiley)
- 26 • EMBASE (Ovid)
- 27 • MEDLINE (Ovid)
- 28 • MEDLINE In-Process (Ovid)

2.2.1 Identification of evidence for clinical questions

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

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

34 Review question 1:

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

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

39 Search Strategy:

40 -----

41 1 exp Gastroesophageal Reflux/ (21027)

42 2 exp Duodenogastric Reflux/ (1565)

- 43 3 (reflux\$ or gord or gerd or ger).tw. (39779)
- 44 4 Esophageal Sphincter, Lower/ (585)
- 45 5 lower esophageal sphincter.tw. (3304)
- 46 6 lower oesophageal sphincter.tw. (912)
- 47 7 (les or los).tw. (17380)
- 48 8 pyros\$.tw. (3794)
- 49 9 acid exposure.tw. (1984)
- 50 10 Dyspepsia/ (7027)
- 51 11 (dyspep\$ or indigestion\$).tw. (10106)
- 52 12 (regurg\$ or waterbrash\$).tw. (25130)
- 53 13 hypergastrin*.tw. (1546)
- 54 14 Heartburn/ (1642)
- 55 15 heartburn\$.tw. (3654)
- 56 16 exp Abdominal Pain/ (24380)
- 57 17 ((abdom\$ or stomach\$) adj3 (ache\$ or pain\$ or discomfort\$)).tw. (36640)
- 58 18 Chest Pain/ (8711)
- 59 19 ((chest\$ or thora\$) adj3 (ache\$ or pain\$ or discomfort\$)).tw. (24251)
- 60 20 (epigastri\$ adj3 (ache\$ or pain\$ or discomfort\$)).tw. (3381)
- 61 21 or/1-20 (179328)
- 62 22 exp Endoscopy, Digestive System/ (78303)
- 63 23 (endoscop\$ or gastroscop\$ or videoscop\$).tw. (126962)
- 64 24 chromoendoscop\$.tw. (532)
- 65 25 (esophagoscop\$ or oesophagoscop\$).tw. (1762)
- 66 26 or/22-25 (162901)
- 67 27 21 and 26 (19121)
- 68 28 risk factors/ (523427)
- 69 29 risk\$.tw. (1123252)
- 70 30 "Signs and Symptoms"/ (422)
- 71 31 (sign* adj symptom*).tw. (3497)
- 72 32 or/28-31 (1317377)
- 73 33 27 and 32 (2631)
- 74 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 50 ((gastro-oesophageal\$ or gastrooesophageal\$ or gastroesophageal\$ or gastro-
91 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)

- 107 66 Body Weight/ (156681)
108 67 exp Overweight/ (130992)
109 68 (weight\$ or overweight\$ or obes\$ or body fat).tw. (727583)
110 69 or/64-68 (885805)
111 70 27 and 69 (1665)
112 71 Age Factors/ (358134)
113 72 Aging/ (180363)
114 73 Geriatrics/ (26146)
115 74 exp Aged/ (2211124)
116 75 Middle Aged/ (3144169)
117 76 (age\$ or aging or elder\$ or geriatric\$ or old\$).tw. (2842713)
118 77 or/71-76 (5532610)
119 78 33 and 77 (1944)
120 79 Sex/ (7197)
121 80 Sex Factors/ (202377)
122 81 Men/ (2535)
123 82 Women/ (13200)
124 83 (sex or sexes or gender\$ or male\$ or female\$ or man or woman or women or men).tw.
125 (2090224)
126 84 or/79-83 (2174250)
127 85 33 and 84 (883)
128 86 exp Population Groups/ (197033)
129 87 eh.fs. (115162)
130 88 (ethnic\$ or ethno\$ or race\$ or racial\$).tw. (155305)
131 89 or/86-88 (342359)
132 90 27 and 89 (278)
133 91 animals/ not humans/ (3753959)
134 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)
135 93 92 not 91 (6294)
136 94 limit 93 to english language (5150)
137 95 incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos:.tw. or predict:.tw. or
138 course:.tw. (2070024)
139 96 (sensitiv: or diagnos:).mp. or di.fs. (3656151)

140 97 95 or 96 (5064379)

141 98 94 and 97 (3567)

142

143 **Review Question 2:**

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

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

147 Search Strategy:

148 -----

149 1 Barrett Esophagus/ (5715)

150 2 barrett\$.tw. (6721)

151 3 ((column\$ or speciali\$ or intestinali\$) adj3 (epithel\$ or oesophag\$ or esophag\$ or
152 mucos\$)).tw. (4244)

153 4 or/1-3 (10763)

154 5 exp Endoscopy/ (238917)

155 6 (endoscop\$ or gastroscop\$ or videoscop\$).tw. (124065)

156 7 chromoendoscop\$.tw. (519)

157 8 (esophagoscop\$ or oesophagoscop\$).tw. (1758)

158 9 or/5-8 (287817)

159 10 4 and 9 (3856)

160 11 risk factors/ (508949)

161 12 risk\$.tw. (1087586)

162 13 or/11-12 (1274619)

163 14 10 and 13 (1162)

164 15 exp Hernia/ (58747)

165 16 (hernia\$ or enterocele\$).tw. (47909)

166 17 15 or 16 (71245)

167 18 10 and 17 (365)

168 19 Eructation/ (277)

169 20 (eructat\$ or belch\$ or burp\$).tw. (971)

170 21 19 or 20 (1080)

171 22 10 and 21 (12)

- 172 23 Chest Pain/ (8520)
173 24 ((chest or thora\$) adj3 (pain\$ or ache\$ or discomfort\$)).tw. (23936)
174 25 Heartburn/ (1544)
175 26 (heartburn\$ or pyros\$).tw. (6731)
176 27 or/23-26 (33421)
177 28 10 and 27 (308)
178 29 bile\$ reflux\$.tw. (683)
179 30 10 and 29 (40)
180 31 ((gastro-oesophageal\$ or gastrooesophageal\$ or gastroesophageal\$ or gastro-
181 esophageal\$) adj junction\$).tw. (1880)
182 32 10 and 31 (181)
183 33 exp Diet/ (178565)
184 34 (diet\$ or food\$ or nutrition\$).tw. (619496)
185 35 33 or 34 (682299)
186 36 10 and 35 (78)
187 37 exp Smoking/ (113322)
188 38 (smok\$ or cigarette\$ or cigar\$ or tobacco\$).tw. (197081)
189 39 37 or 38 (224058)
190 40 10 and 39 (117)
191 41 exp Drinking Behavior/ (53005)
192 42 (alcohol\$ or drink\$).tw. (255109)
193 43 or/41-42 (266547)
194 44 10 and 43 (100)
195 45 body mass index/ (69217)
196 46 (body mass index\$ or bmi\$ or quetelet\$ index\$).tw. (105391)
197 47 Body Weight/ (155285)
198 48 exp Overweight/ (127354)
199 49 (weight\$ or overweight\$ or obes\$ or body fat).tw. (710695)
200 50 or/45-49 (865676)
201 51 10 and 50 (184)
202 52 Age Factors/ (353281)
203 53 Aging/ (177973)

204 54 Geriatrics/ (26016)
205 55 exp Aged/ (2177675)
206 56 Middle Aged/ (3096169)
207 57 (age\$ or aging or elder\$ or geriatric\$ or old\$).tw. (2782636)
208 58 or/52-57 (5441703)
209 59 14 and 58 (688)
210 60 Sex/ (7245)
211 61 Sex Factors/ (198826)
212 62 Men/ (2516)
213 63 Women/ (13143)
214 64 (sex or sexes or gender\$ or male\$ or female\$ or man or woman or women or men).tw.
215 (2049175)
216 65 or/60-64 (2132677)
217 66 14 and 65 (303)
218 67 exp Population Groups/ (191780)
219 68 eh.fs. (112002)
220 69 (ethnic\$ or ethno\$ or race\$ or racial\$).tw. (150638)
221 70 or/67-69 (333290)
222 71 10 and 70 (90)
223 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)
224 73 limit 72 to english language (1616)
225 74 animals/ not humans/ (3717557)
226 75 73 not 74 (1607)

227

228 **Review Question 3:**

229

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

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

234 Search Strategy:

235

236 -----

- 237 1 Dyspepsia/ (6821)
- 238 2 (dyspep\$ or indigestion\$).tw. (9703)
- 239 3 waterbrash\$.tw. (8)
- 240 4 (regurg\$ not (mitral\$ or vascular\$ or pulmonar\$)).tw. (9577)
- 241 5 Heartburn/ (1513)
- 242 6 heartburn\$.tw. (3370)
- 243 7 pyros\$.tw. (2949)
- 244 8 acid exposure.tw. (1851)
- 245 9 exp Esophagitis/ (8912)
- 246 10 (esophagit\$ or oesophagit\$).tw. (10353)
- 247 11 exp Gastritis/ (17242)
- 248 12 (gastrit\$ or gastr\$ stas\$).tw. (16167)
- 249 13 exp Gastroesophageal Reflux/ (20000)
- 250 14 exp Duodenogastric Reflux/ (1550)
- 251 15 (gord or gerd or ger).tw. (6617)
- 252 16 reflux\$.tw. (37107)
- 253 17 Esophageal Sphincter, Lower/ (510)
- 254 18 lower esophageal sphincter.tw. (3226)
- 255 19 lower oesophageal sphincter.tw. (901)
- 256 20 or/1-19 (92751)
- 257 21 Consultants/ (5573)
- 258 22 Specialization/ (20669)
- 259 23 Gastroenterology/ (7308)
- 260 24 (consultant\$ or speciali\$ or gastroenterolog\$ or proctolog\$ or expert\$).tw. (217588)
- 261 25 exp Hospitals/ (186342)
- 262 26 exp Hospital Units/ (69860)
- 263 27 exp Hospitalization/ (141259)
- 264 28 hospital\$.tw. (696207)
- 265 29 (tertiary-care or secondary-care).tw. (21389)
- 266 30 ((tertiary or secondary) adj3 (care or service\$ or center\$ or centre\$ or practice\$)).tw.
267 (35460)
- 268 31 General Surgery/ (31930)

- 269 32 exp Surgical Procedures, Operative/ (2199124)
270 33 (surg\$ or operation\$ or operative\$).tw. (1380905)
271 34 Outpatients/ (7494)
272 35 Outpatient Clinics, Hospital/ (13781)
273 36 (outpatient\$ or out-patient\$).tw. (103405)
274 37 Inpatients/ (10895)
275 38 (inpatient\$ or in-patient\$).tw. (996267)
276 39 or/21-38 (4345444)
277 40 20 and 39 (46928)
278 41 exp "Referral and Consultation"/ (52336)
279 42 (refer or referr\$ or consult\$ or second opinion\$ or gatekeep\$).tw. (234511)
280 43 41 or 42 (259007)
281 44 40 and 43 (2168)
282 45 Ambulatory Care/ or ambulatory care facilities/ (44134)
283 46 Primary Health Care/ (48213)
284 47 exp General Practice/ (61347)
285 48 General Practitioners/ (933)
286 49 Physicians, Family/ (14316)
287 50 Physicians, Primary Care/ (605)
288 51 gp\$.tw. (97800)
289 52 ((general or family) adj (practice\$ or practitioner\$ or physician\$ or doctor\$)).tw. (72469)
290 53 primary-care.tw. (57220)
291 54 ((primary or ambulatory) adj3 (care or health\$ or service\$ or center\$ or centre\$ or
292 practice\$)).tw. (87434)
293 55 Community Health Services/ (25377)
294 56 Community health nursing/ (17833)
295 57 ((walkin or walk-in or "walk in" or community health) adj3 (care or service\$ or centre\$ or
296 center\$ or clinic\$ or facilit\$)).tw. (4417)
297 58 or/45-57 (348834)
298 59 20 and 43 and 58 (483)
299 60 44 or 59 (2283)
300 61 animals/ not humans/ (3663211)
301 62 60 not 61 (2262)

302 63 limit 62 to english language (1950)

303

304 **Review Question 4:**

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

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

309 Search Strategy:

310 -----

311 1 exp Gastroesophageal Reflux/ (20185)

312 2 exp Duodenogastric Reflux/ (1555)

313 3 (reflux\$ or gord or gerd or ger).tw. (38474)

314 4 exp Esophagitis/ (8968)

315 5 (esophagi\$ or oesophagi\$).tw. (10838)

316 6 exp Gastritis/ (17333)

317 7 (gastrit\$ or gastr\$ stas\$).tw. (16290)

318 8 or/1-7 (71512)

319 9 Proton Pump Inhibitors/ (2506)

320 10 Omeprazole/ (8164)

321 11 (ppi\$ or proton pump\$ or omeprazole\$ or losec\$ or rabeprazole\$ or pariet\$ or
322 pantoprazole\$ or protium\$ or lansoprazole\$ or zoton\$ or esomeprazole\$ or nexium\$ or
323 emozul\$).tw. (65237)

324 12 or/9-11 (67160)

325 13 8 and 12 (6324)

326

327 **Review Question 5:**

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

330 Database: Ovid MEDLINE(R) <1946 to August Week 5 2012> (update search conducted on
331 02 December 2013)

332 Search Strategy:

333 -----

334 1 sequen\$.tw. (807727)

335 2 tripl\$.tw. (59536)

- 336 3 quadrupl\$.tw. (6797)
- 337 4 ((standard\$ or convention\$) adj3 (therap\$ or treat\$ or regim\$)).tw. (75690)
- 338 5 or/1-4 (935763)
- 339 6 Proton Pump Inhibitors/ (2485)
- 340 7 Omeprazole/ (8152)
- 341 8 (ppi\$ or proton pump\$ or omeprazole\$ or losec\$ or rabeprazole\$ or pariet\$ or
342 pantoprazole\$ or protium\$ or lansoprazole\$ or zoton\$ or esomeprazole\$ or nexium\$).tw.
343 (65001)
- 344 9 or/6-8 (66918)
- 345 10 exp Nitroimidazoles/ (14617)
- 346 11 (nitroimidazole\$ or antiprotozoal\$ or metronidazole\$ or flagyl\$ or tinidazole\$ or
347 fasigyn\$).tw. (13291)
- 348 12 Clarithromycin/ (4687)
- 349 13 (clarithromycin\$ or klaricid\$).tw. (5916)
- 350 14 exp Amoxicillin/ (8612)
- 351 15 (amox\$ or amix\$ or amoram\$ or amoxident\$ or alenamox\$ or rimoxallin\$).tw. (12013)
- 352 16 Bismuth/ (4535)
- 353 17 (bismuth\$ or tripotassium\$ or tri-potassium\$ or tri potassium\$ or de-noltab\$ or
354 denoltab\$ or de noltab\$).tw. (4269)
- 355 18 exp Tetracyclines/ (38584)
- 356 19 tetracyclin\$.tw. (25722)
- 357 20 exp Quinolones/ (32885)
- 358 21 (quinolon\$ or levofloxacin\$ or tavinic\$ or moxifloxacin\$ or avelox\$).tw. (13701)
- 359 22 or/10-21 (122402)
- 360 23 9 and 22 (3088)
- 361 24 5 or 23 (937359)
- 362 25 exp Helicobacter/ (27735)
- 363 26 Helicobacter Infections/ (22948)
- 364 27 exp Campylobacter/ (9249)
- 365 28 (helicobac\$ or campylobact\$ or pylori\$).tw. (48325)
- 366 29 or/25-28 (51267)
- 367 30 24 and 29 (7232)

368 Update search conducted on PubMed on 02 December 2013

369 Strategy:

National Institute for Health and Care Excellence 2014.

- 370 Search (#11 or #12)
- 371 Search (#9 AND publisher [sb])
- 372 Search (#9 AND #10)
- 373 Search ("2013/10/10"[Date - Entrez] : "3000"[Date - Entrez])
- 374 Search (#7 and #8)
- 375 Search (helicobac* or campylobact* or pylori*[Title/Abstract])
- 376 Search (#3 or #6)
- 377 Search (#4 and #5)
- 378 Search (#1 or #2)
- 379 Search (nitroimidazole* or antiprotozoal* or metronidazole* or flagyl* or tinidazole* or
380 fasigyn* or clarithromycin* or klaricid* or amox* or amix* or amoram* or amoxidant* or
381 alenamox* or rimoxallin* or bismuth* or tripotassium* or tri-potassium* or tri potassium* or
382 de-noltab* or denoltab* or de noltab* or tetracyclin* or quinolon* or levofloxacin* or tavinic* or
383 moxifloxacin* or avelox*[Title/Abstract])
- 384 Search (ppi* or proton pump* or omeprazole* or losec* or rabeprazole* or pariet* or
385 pantoprazole* or protium* or lansoprazole* or zoton* or esomeprazole* or
386 nexium*[Title/Abstract])
- 387 Search (standard* OR convention* AND therap* OR treat* OR regim*[Title/Abstract])
- 388 Search (sequen* or tripl* or quadrupl*[Title/Abstract])
- 389
- 390 **Review Question 6:**
- 391 What is the effectiveness of laparoscopic fundoplication compared to medical management
392 in patients with GORD?
- 393 Database: Ovid MEDLINE(R) <1948 to November Week 3 2011> (update search conducted
394 on 17 December 2013)
- 395 Search Strategy:
396 -----
- 397 1 exp Gastroesophageal Reflux/ (19796)
- 398 2 exp Duodenogastric Reflux/ (1567)
- 399 3 (reflux\$ or gord or gerd or ger).tw. (37759)
- 400 4 Esophageal Sphincter, Lower/ (466)
- 401 5 lower esophageal sphincter.tw. (3192)
- 402 6 lower oesophageal sphincter.tw. (893)
- 403 7 (les or los).tw. (15977)

- 404 8 Heartburn/ (1461)
405 9 heartburn\$.tw. (3294)
406 10 pyros\$.tw. (2439)
407 11 acid exposure.tw. (1801)
408 12 Dyspepsia/ (6800)
409 13 (dyspep\$ or indigestion\$).tw. (9598)
410 14 (regurg\$ or waterbrash\$).tw. (23945)
411 15 exp Esophagitis/ (8866)
412 16 (esophagi\$ or oesophagi\$).tw. (10675)
413 17 exp Gastritis/ (17444)
414 18 (gastrit\$ or gastr\$ stas\$).tw. (16251)
415 19 or/1-18 (120456)
416 20 Fundoplication/ (3123)
417 21 fundoplicat\$.tw. (3941)
418 22 gastroplicat\$.tw. (50)
419 23 nissen.tw. (2208)
420 24 (toupet or lind or watson or besley or hill).tw. (15508)
421 25 (antireflux\$ or anti-reflux\$ or anti reflux\$).tw. (4362)
422 26 or/20-25 (22949)
423 27 19 and 26 (6329)

424

425 **Review Question 7:**

426

427 What other medical management is effective for patients who do not respond to
428 PPIs, H₂ receptor antagonists, or *H pylori* eradication despite optimum primary care,
429 or patients who have relapsed following surgery?

430

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

433 Search Strategy:

434 -----

- 435 1 exp Gastroesophageal Reflux/ (20261)
- 436 2 exp Duodenogastric Reflux/ (1555)
- 437 3 (reflux\$ or gord or gerd or ger).tw. (38634)
- 438 4 Esophageal Sphincter, Lower/ (536)
- 439 5 lower esophageal sphincter.tw. (3257)
- 440 6 lower oesophageal sphincter.tw. (907)
- 441 7 (les or los).tw. (16703)
- 442 8 Heartburn/ (1538)
- 443 9 heartburn\$.tw. (3422)
- 444 10 pyros\$.tw. (3254)
- 445 11 acid exposure.tw. (1885)
- 446 12 Dyspepsia/ (6883)
- 447 13 (dyspep\$ or indigestion\$).tw. (9823)
- 448 14 (regurg\$ or waterbrash\$).tw. (24575)
- 449 15 exp Esophagitis/ (9004)
- 450 16 (esophagi\$ or oesophagi\$).tw. (10881)
- 451 17 exp Gastritis/ (17381)
- 452 18 (gastrit\$ or gastr\$ stas\$).tw. (16348)
- 453 19 exp Abdominal Pain/ (23831)
- 454 20 ((abdom\$ or stomach\$) adj3 (ache\$ or pain\$ or discomfort\$)).tw. (35707)
- 455 21 or/1-20 (172460)
- 456 22 Proton Pump Inhibitors/ (2569)
- 457 23 Omeprazole/ (8191)
- 458 24 (ppi\$ or proton pump\$ or omeprazole\$ or losec\$ or rabeprazole\$ or pariet\$ or
- 459 pantoprazole\$ or protium\$ or lansoprazole\$ or zoton\$ or esomeprazole\$ or nexium\$ or
- 460 emozul\$).tw. (65637)
- 461 25 or/22-24 (67572)
- 462 26 (nocturn\$ or night\$ or evening\$ or bed\$ or sleep\$).tw. (246121)
- 463 27 ((split\$ or separat\$ or divi\$ or even\$ or spread\$ or multipl\$ or alter\$ or chang\$ or
- 464 reduc\$ or less\$ or small\$ or low\$) adj3 dos\$).tw. (196251)
- 465 28 25 and (26 or 27) (2830)
- 466 29 21 and 28 (753)
- 467 30 exp Histamine H2 Antagonists/ (18029)

- 468 31 (h2ra\$ or h2-ra\$ or "h2 ra\$").tw. (413)
- 469 32 (histamin\$ adj3 (antagon\$ or block\$ or recep\$)).tw. (11117)
- 470 33 (h2\$ adj3 (antagon\$ or hist\$ or block\$ or recep\$)).tw. (14520)
- 471 34 cimetidin\$.tw. (10207)
- 472 35 tagamet.tw. (95)
- 473 36 ranitidin\$.tw. (5384)
- 474 37 zantac.tw. (56)
- 475 38 famotidin\$.tw. (1635)
- 476 39 nizatidin\$.tw. (354)
- 477 40 axid.tw. (10)
- 478 41 or/30-40 (35084)
- 479 42 25 and 41 (3913)
- 480 43 21 and 42 (1495)
- 481 44 Dopamine Antagonists/ (9263)
- 482 45 (dopamin\$ adj3 (receptor\$ or antagonist\$)).tw. (27446)
- 483 46 prokinetic\$.tw. (1882)
- 484 47 Metoclopramide/ (4448)
- 485 48 (metoclopramide or maxolon).tw. (4925)
- 486 49 Domperidone/ (1503)
- 487 50 (domperidone or motilium).tw. (1835)
- 488 51 (itopride or ganaton).tw. (64)
- 489 52 (mosapride or bionus).tw. (187)
- 490 53 or/44-52 (38965)
- 491 54 21 and 53 (1474)
- 492 55 exp Laparoscopy/ (62058)
- 493 56 laparoscopes/ (3291)
- 494 57 surgical procedures, Minimally Invasive/ (15264)
- 495 58 (laparoscop\$ or celioscop\$ or keyhole\$).tw. (72639)
- 496 59 or/55-58 (95003)
- 497 60 Fundoplication/ (3277)
- 498 61 fundoplicat\$.tw. (4067)
- 499 62 gastroplicat\$.tw. (48)

- 500 63 nissen.tw. (2247)
- 501 64 (toupet or lind or watson or besley or hill).tw. (15936)
- 502 65 (antireflux\$ or anti-reflux\$ or anti reflux\$).tw. (4397)
- 503 66 or/60-65 (23538)
- 504 67 59 and 66 (2960)
- 505 68 21 and 67 (2290)
- 506 69 29 or 43 or 54 or 68 (5510)

507

508 **Review Question 8:**

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

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

513 Search Strategy:

514 -----

- 515 1 Barrett Esophagus/ (5504)
- 516 2 barrett\$.tw. (6461)
- 517 3 ((column\$ or speciali\$ or intestinali\$) adj3 (epithel\$ or oesophag\$ or esophag\$ or
518 mucos\$)).tw. (4142)
- 519 4 ((metaplas\$ or dysplasi\$ or neoplasia\$) adj3 (column\$ or intestin\$ or epithel\$ or
520 oesophag\$ or esophag\$ or mucos\$ or high-grade\$ or low-grade\$)).tw. (13822)
- 521 5 or/1-4 (21574)
- 522 6 exp Mass Screening/ (90868)
- 523 7 exp Population Surveillance/ (44090)
- 524 8 (screen\$ or surveillan\$ or monitor\$).tw. (843147)
- 525 9 or/6-8 (896405)
- 526 10 exp Endoscopy/ (231412)
- 527 11 endoscop\$.tw. (116970)
- 528 12 chromoendoscop\$.tw. (489)
- 529 13 (esophagoscop\$ or oesophagoscop\$).tw. (1731)
- 530 14 exp Biopsy/ (205812)
- 531 15 biops\$.tw. (251781)
- 532 16 or/10-15 (604770)

- 533 17 9 and 16 (43493)
- 534 18 5 and 17 (2222)
- 535 **Broad update search for all review questions (apart from RQ5) conducted on PubMed**
536 **on 11 December 2013**
- 537 Strategy:
- 538 Search (#21 or #23)
- 539 Search (#19 and #20)
- 540 Search (#19 and #22)
- 541 Search ("2013/12/09"[Date - Entrez] : "3000"[Date - Entrez])
- 542 Search publisher[sb]
- 543 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
544 or #15 or #16 or #17 or #18)
- 545 Search ((metaplas* or dysplasi* or neoplas*[Title/Abstract])) AND (epithel* or oesophag* or
546 esophag* or mucos*[Title/Abstract])
- 547 Search ((column* or speciali* or intestinali*[Title/Abstract])) AND (epithel* or oesophag* or
548 esophag* or mucos*[Title/Abstract])
- 549 Search (((((reflux*[Title/Abstract]) NOT (coronar* or heart* or mitral* or vascular* or
550 pulmonar* or vesico* or uter* or laryn*[Title/Abstract])))
- 551 Search lower esophageal sphincter[Title/Abstract]
- 552 Search lower oesophageal sphincter[Title/Abstract]
- 553 Search pyros*[Title/Abstract]
- 554 Search acid exposure[Title/Abstract]
- 555 Search esophagit*[Title/Abstract]
- 556 Search oesophagit*[Title/Abstract]
- 557 Search gord[Title/Abstract]
- 558 Search gerd[Title/Abstract]
- 559 Search ger[Title/Abstract]
- 560 Search indigestion*[Title/Abstract]
- 561 Search barrett*[Title/Abstract]
- 562 Search heartburn[Title/Abstract]
- 563 Search (((acid*[Title/Abstract]) AND regurg*[Title/Abstract]))
- 564 Search dyspep*[Title/Abstract]
- 565 Search waterbrash*[Title/Abstract]

562.2.2 Study design filters

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

570 Specific systematic reviews filter

571 *Appended to review questions 4 and 7*

- 572 1 Meta-Analysis.pt. (37837)
- 573 2 Meta-Analysis as Topic/ (12594)
- 574 3 (metaanaly\$ or metanaly\$ or (meta adj2 analy\$)).tw. (45065)
- 575 4 (systematic\$ adj4 (review\$ or overview\$)).tw. (40425)
- 576 5 ((quantitative\$ or qualitative\$) adj4 (review\$ or overview\$)).tw. (3110)
- 577 6 ((studies or trial\$) adj1 (review\$ or overview\$)).tw. (6557)
- 578 7 (integrat\$ adj2 (research or review\$ or literature)).tw. (3111)
- 579 8 (pool\$ adj1 (analy\$ or data)).tw. (7682)
- 580 9 (handsearch\$ or (hand adj2 search\$)).tw. (4484)
- 581 10 (manual\$ adj2 search\$).tw. (2443)
- 582 11 or/1-10 (105950)

583

584 Broad systematic reviews filter

585 *Appended to review questions 5 and 6*

- 586 1 Meta-Analysis.pt. (37837)
- 587 2 Meta-Analysis as Topic/ (12594)
- 588 3 Review.pt. (1757173)
- 589 4 exp Review Literature as Topic/ (6618)
- 590 5 (metaanaly\$ or metanaly\$ or (meta adj2 analy\$)).tw. (45065)
- 591 6 (review\$ or overview\$).ti. (240634)
- 592 7 (systematic\$ adj4 (review\$ or overview\$)).tw. (40425)
- 593 8 ((quantitative\$ or qualitative\$) adj4 (review\$ or overview\$)).tw. (3110)
- 594 9 ((studies or trial\$) adj1 (review\$ or overview\$)).tw. (6557)
- 595 10 (integrat\$ adj2 (research or review\$ or literature)).tw. (3111)
- 596 11 (pool\$ adj1 (analy\$ or data)).tw. (7682)
- 597 12 (handsearch\$ or (hand adj2 search\$)).tw. (4484)
- 598 13 (manual\$ adj2 search\$).tw. (2443)

- 599 14 or/1-13 (1894766)
- 600 **Specific RCT filter**
- 601 *Appended to review questions 4 and 7*
- 602 1 Randomized Controlled Trial.pt. (342057)
- 603 2 Controlled Clinical Trial.pt. (85675)
- 604 3 Placebos/ (31568)
- 605 4 Random Allocation/ (76571)
- 606 5 Double-Blind Method/ (118432)
- 607 6 Single-Blind Method/ (17072)
- 608 7 Cross-Over Studies/ (30968)
- 609 8 ((random\$ or control\$ or clinical\$) adj2 (trial\$ or stud\$)).tw. (569547)
- 610 9 (random\$ adj2 allocat\$).tw. (18127)
- 611 10 placebo\$.tw. (141042)
- 612 11 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw. (116052)
- 613 12 (crossover\$ or (cross adj over\$)).tw. (52321)
- 614 13 or/1-12 (945299)
- 615 **Broad RCT filter**
- 616 *Appended to review questions 5 and 6*
- 617 1 Randomized Controlled Trial.pt. (342057)
- 618 2 Controlled Clinical Trial.pt. (85675)
- 619 3 Clinical Trial.pt. (476279)
- 620 4 exp Clinical Trials as Topic/ (264246)
- 621 5 Placebos/ (31568)
- 622 6 Random Allocation/ (76571)
- 623 7 Double-Blind Method/ (118432)
- 624 8 Single-Blind Method/ (17072)
- 625 9 Cross-Over Studies/ (30968)
- 626 10 ((random\$ or control\$ or clinical\$) adj2 (trial\$ or stud\$)).tw. (569547)
- 627 11 (random\$ adj2 allocat\$).tw. (18127)
- 628 12 placebo\$.tw. (141042)
- 629 13 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw. (116052)

- 630 14 (crossover\$ or (cross adj over\$)).tw. (52321)
631 15 or/1-14 (1198484)
632 16 animals/ not humans/ (3718637)
633 17 15 not 16 (1120965)

634.2.3 Economic evaluations and quality of life data

635 Sources searched to identify economic evaluations

- 636 • NHS Economic Evaluation Database – NHS EED (Wiley)
- 637 • Health Economic Evaluations Database – HEED (Wiley)
- 638 • Embase (Ovid)
- 639 • MEDLINE (Ovid)
- 640 • MEDLINE In-Process (Ovid)

641 Health economics studies on dyspepsia and GORD

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

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

645 Search Strategy:

646 -----

- 647 1 Dyspepsia/ (6726)
648 2 (dyspep\$ or indigestion\$).tw. (9523)
649 3 (regurg\$ or waterbrash\$).tw. (23471)
650 4 Heartburn/ (1468)
651 5 heartburn\$.tw. (3288)
652 6 pyros\$.tw. (2421)
653 7 acid exposure.tw. (1804)
654 8 exp Peptic Ulcer/ (70434)
655 9 ((peptic\$ or gastr\$ or duoden\$ or stomach\$) adj3 ulcer\$).tw. (50958)
656 10 exp Esophagitis/ (8754)
657 11 (esophagi\$ or oesophagi\$).tw. (10524)
658 12 exp Gastritis/ (17049)
659 13 (gastrit\$ or gastr\$ stas\$).tw. (15913)
660 14 exp Gastroesophageal Reflux/ (19636)

- 661 15 exp Duodenogastric Reflux/ (1533)
662 16 (reflux\$ or gord or gerd or ger).tw. (37306)
663 17 Esophageal Sphincter, Lower/ (467)
664 18 lower esophageal sphincter.tw. (3160)
665 19 lower oesophageal sphincter.tw. (892)
666 20 (les or los).tw. (15672)
667 21 or/1-20 (183837)
668 22 exp Gastrointestinal Neoplasms/ (251799)
669 23 ((stomach\$ or oesoph\$ or esoph\$ or intestin\$ or gastric\$) adj3 (cancer\$ or carcinoma\$
670 or adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (82446)
671 24 ((upper digestive\$ or upper gastr\$ or upper gi) adj3 (cancer\$ or carcinoma\$ or
672 adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (1286)
673 25 or/22-24 (264951)
674 26 21 or 25 (428356)

675 **Health economics studies for Barrett's oesophagus**

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

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

679 Search Strategy:

680 -----

- 681 1 Barrett Esophagus/ (5527)
682 2 barrett\$.tw. (6488)
683 3 ((column\$ or speciali\$ or intestinali\$) adj3 (epithel\$ or oesophag\$ or esophag\$ or
684 mucos\$)).tw. (4149)
685 4 ((metaplas\$ or dysplasi\$ or neoplasia\$) adj3 (column\$ or intestin\$ or epithel\$ or
686 oesophag\$ or esophag\$ or mucos\$ or high-grade\$ or low-grade\$)).tw. (13859)
687 5 or/1-4 (21633)

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

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

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

694 Search Strategy:

695 -----

- 696 1 exp Gastroesophageal Reflux/ (21073)
- 697 2 exp Duodenogastric Reflux/ (1566)
- 698 3 (reflux\$ or gord or gerd or ger).tw. (39865)
- 699 4 Esophageal Sphincter, Lower/ (589)
- 700 5 lower esophageal sphincter.tw. (3312)
- 701 6 lower oesophageal sphincter.tw. (912)
- 702 7 (les or los).tw. (17474)
- 703 8 pyros\$.tw. (3852)
- 704 9 acid exposure.tw. (1990)
- 705 10 Dyspepsia/ (7033)
- 706 11 (dyspep\$ or indigestion\$).tw. (10122)
- 707 12 (regurg\$ or waterbrash\$).tw. (25208)
- 708 13 hypergastrin*.tw. (1550)
- 709 14 Heartburn/ (1650)
- 710 15 heartburn\$.tw. (3667)
- 711 16 exp Abdominal Pain/ (24439)
- 712 17 ((abdom\$ or stomach\$) adj3 (ache\$ or pain\$ or discomfort\$)).tw. (36738)
- 713 18 Chest Pain/ (8747)
- 714 19 ((chest\$ or thora\$) adj3 (ache\$ or pain\$ or discomfort\$)).tw. (24330)
- 715 20 (epigastri\$ adj3 (ache\$ or pain\$ or discomfort\$)).tw. (3388)
- 716 21 or/1-20 (179880)
- 717 22 exp Endoscopy, Digestive System/ (78532)
- 718 23 (endoscop\$ or gastroscop\$ or videoscop\$).tw. (127383)
- 719 24 chromoendoscop\$.tw. (533)
- 720 25 (esophagoscop\$ or oesophagoscop\$).tw. (1764)
- 721 26 or/22-25 (163419)
- 722 27 21 and 26 (19172)
- 723 28 risk factors/ (525551)
- 724 29 risk\$.tw. (1128239)
- 725 30 "Signs and Symptoms"/ (422)
- 726 31 (sign* adj symptom*).tw. (3508)
- 727 32 or/28-31 (1322964)

- 728 33 27 and 32 (2645)
- 729 34 exp Hernia/ (59410)
- 730 35 (hernia\$ or enterocele\$).tw. (48852)
- 731 36 34 or 35 (72210)
- 732 37 27 and 36 (1248)
- 733 38 Eructation/ (281)
- 734 39 (eructat\$ or belch\$ or burp\$).tw. (998)
- 735 40 38 or 39 (11111)
- 736 41 27 and 40 (126)
- 737 42 Polymorphism, Single Nucleotide/ (57063)
- 738 43 single nucleotide polymorphism.tw. (12199)
- 739 44 or/42-43 (59882)
- 740 45 27 and 44 (11)
- 741 46 ((paediatric or pediatric) adj reflux\$).tw. (9)
- 742 47 27 and 46 (1)
- 743 48 (famil* adj history).tw. (38382)
- 744 49 27 and 48 (137)
- 745 50 ((gastro-oesophageal\$ or gastrooesophageal\$ or gastroesophageal\$ or gastro-
746 esophageal\$) adj junction\$).tw. (1937)
- 747 51 27 and 50 (332)
- 748 52 exp Diet/ (183353)
- 749 53 (diet\$ or food\$ or nutrition\$).tw. (636973)
- 750 54 52 or 53 (700671)
- 751 55 27 and 54 (1154)
- 752 56 exp Smoking/ (115460)
- 753 57 (smok\$ or cigarette\$ or cigar\$ or tobacco\$).tw. (201772)
- 754 58 56 or 57 (229102)
- 755 59 27 and 58 (484)
- 756 60 exp Drinking Behavior/ (54157)
- 757 61 (alcohol\$ or drink\$).tw. (260642)
- 758 62 or/60-61 (272215)
- 759 63 27 and 62 (559)

- 760 64 body mass index/ (72497)
761 65 (body mass index\$ or bmi\$ or quetelet\$ index\$.tw. (110696)
762 66 Body Weight/ (156912)
763 67 exp Overweight/ (131550)
764 68 (weight\$ or overweight\$ or obes\$ or body fat).tw. (729928)
765 69 or/64-68 (888634)
766 70 27 and 69 (1677)
767 71 Age Factors/ (358917)
768 72 Aging/ (180659)
769 73 Geriatrics/ (26153)
770 74 exp Aged/ (2217442)
771 75 Middle Aged/ (3152892)
772 76 (age\$ or aging or elder\$ or geriatric\$ or old\$.tw. (2851598)
773 77 or/71-76 (5547763)
774 78 33 and 77 (1955)
775 79 Sex/ (7200)
776 80 Sex Factors/ (202863)
777 81 Men/ (2537)
778 82 Women/ (13211)
779 83 (sex or sexes or gender\$ or male\$ or female\$ or man or woman or women or men).tw.
780 (2096355)
781 84 or/79-83 (2180475)
782 85 33 and 84 (886)
783 86 exp Population Groups/ (197734)
784 87 eh.fs. (115535)
785 88 (ethnic\$ or ethno\$ or race\$ or racial\$.tw. (155957)
786 89 or/86-88 (343593)
787 90 27 and 89 (280)

788 **Health economics questions on Q2: Symptoms indicating endoscopy for Barrett's**
789 **oesophagus plus economic evaluations filter**
790 The searches were undertaken in January 2013. Search filters to retrieve economic
791 evaluations and quality of life papers were appended to the following search strategy to
792 identify relevant evidence

793 Database: Ovid MEDLINE(R) <1946 to November Week 3 2012>
794 Search Strategy:
795 -----
796 1 Barrett Esophagus/ (5721)
797 2 barrett\$.tw. (6728)
798 3 ((column\$ or speciali\$ or intestinali\$) adj3 (epithel\$ or oesophag\$ or esophag\$ or
799 mucos\$)).tw. (4248)
800 4 or/1-3 (10773)
801 5 exp Endoscopy/ (239333)
802 6 (endoscop\$ or gastroscop\$ or videoscop\$).tw. (124226)
803 7 chromoendoscop\$.tw. (520)
804 8 (esophagoscop\$ or oesophagoscop\$).tw. (1759)
805 9 or/5-8 (288290)
806 10 4 and 9 (3859)
807 11 risk factors/ (509982)
808 12 risk\$.tw. (1089808)
809 13 or/11-12 (1277173)
810 14 10 and 13 (1162)
811 15 exp Hernia/ (58796)
812 16 (hernia\$ or enterocele\$).tw. (47965)
813 17 15 or 16 (71313)
814 18 10 and 17 (365)
815 19 Eructation/ (277)
816 20 (eructat\$ or belch\$ or burp\$).tw. (971)
817 21 19 or 20 (1080)
818 22 10 and 21 (12)
819 23 Chest Pain/ (8528)
820 24 ((chest or thora\$) adj3 (pain\$ or ache\$ or discomfort\$)).tw. (23962)
821 25 Heartburn/ (1546)
822 26 (heartburn\$ or pyros\$).tw. (6758)
823 27 or/23-26 (33479)
824 28 10 and 27 (308)

- 825 29 bile\$ reflux\$.tw. (683)
- 826 30 10 and 29 (40)
- 827 31 ((gastro-oesophageal\$ or gastrooesophageal\$ or gastroesophageal\$ or gastro-
828 esophageal\$) adj junction\$.tw. (1885)
- 829 32 10 and 31 (182)
- 830 33 exp Diet/ (178778)
- 831 34 (diet\$ or food\$ or nutrition\$.tw. (620250)
- 832 35 33 or 34 (683111)
- 833 36 10 and 35 (78)
- 834 37 exp Smoking/ (113467)
- 835 38 (smok\$ or cigarette\$ or cigar\$ or tobacco\$.tw. (197375)
- 836 39 37 or 38 (224382)
- 837 40 10 and 39 (117)
- 838 41 exp Drinking Behavior/ (53104)
- 839 42 (alcohol\$ or drink\$.tw. (255464)
- 840 43 or/41-42 (266912)
- 841 44 10 and 43 (100)
- 842 45 body mass index/ (69416)
- 843 46 (body mass index\$ or bmi\$ or quetelet\$ index\$.tw. (105683)
- 844 47 Body Weight/ (155399)
- 845 48 exp Overweight/ (127702)
- 846 49 (weight\$ or overweight\$ or obes\$ or body fat).tw. (711690)
- 847 50 or/45-49 (866901)
- 848 51 10 and 50 (184)
- 849 52 Age Factors/ (353807)
- 850 53 Aging/ (178208)
- 851 54 Geriatrics/ (26028)
- 852 55 exp Aged/ (2180488)
- 853 56 Middle Aged/ (3100516)
- 854 57 (age\$ or aging or elder\$ or geriatric\$ or old\$.tw. (2786610)
- 855 58 or/52-57 (5449058)
- 856 59 14 and 58 (688)

- 857 60 Sex/ (7245)
- 858 61 Sex Factors/ (199058)
- 859 62 Men/ (2519)
- 860 63 Women/ (13153)
- 861 64 (sex or sexes or gender\$ or male\$ or female\$ or man or woman or women or men).tw.
862 (2053611)
- 863 65 or/60-64 (2137179)
- 864 66 14 and 65 (303)
- 865 67 exp Population Groups/ (192157)
- 866 68 eh.fs. (112208)
- 867 69 (ethnic\$ or ethno\$ or race\$ or racial\$).tw. (150987)
- 868 70 or/67-69 (333935)
- 869 71 10 and 70 (90)

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

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

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

876 Search Strategy:

877 -----

- 878 1 Dyspepsia/ (7104)
- 879 2 (dyspep\$ or indigestion\$).tw. (10283)
- 880 3 waterbrash\$.tw. (9)
- 881 4 (regurg\$ not (mitral\$ or vascular\$ or pulmonar\$)).tw. (10180)
- 882 5 Heartburn/ (1675)
- 883 6 heartburn\$.tw. (3729)
- 884 7 pyros\$.tw. (4408)
- 885 8 acid exposure.tw. (2064)
- 886 9 exp Esophagitis/ (9438)
- 887 10 (esophagit\$ or oesophagit\$).tw. (11129)
- 888 11 exp Gastritis/ (17784)
- 889 12 (gastrit\$ or gastr\$ stas\$).tw. (16950)

- 890 13 exp Gastroesophageal Reflux/ (21360)
- 891 14 exp Duodenogastric Reflux/ (1575)
- 892 15 (gord or gerd or ger).tw. (7359)
- 893 16 reflux\$.tw. (39318)
- 894 17 exp Peptic Ulcer/ (72084)
- 895 18 ((peptic* or marginal* or gastroduodenal* or curling*) adj1 ulcer*).tw. (24585)
- 896 19 Esophageal Sphincter, Lower/ (609)
- 897 20 lower esophageal sphincter.tw. (3349)
- 898 21 lower oesophageal sphincter.tw. (917)
- 899 22 or/1-21 (161641)
- 900 23 Consultants/ (5634)
- 901 24 Specialization/ (21087)
- 902 25 Gastroenterology/ (7659)
- 903 26 (consultant\$ or speciali\$ or gastroenterolog\$ or proctolog\$ or expert\$).tw. (241395)
- 904 27 exp Hospitals/ (194688)
- 905 28 exp Hospital Units/ (74766)
- 906 29 exp Hospitalization/ (151911)
- 907 30 hospital\$.tw. (744975)
- 908 31 (tertiary-care or secondary-care).tw. (24034)
- 909 32 ((tertiary or secondary) adj3 (care or service\$ or center\$ or centre\$ or practice\$)).tw.
910 (39887)
- 911 33 General Surgery/ (32747)
- 912 34 exp Surgical Procedures, Operative/ (2314506)
- 913 35 (surg\$ or operation\$ or operative\$).tw. (1462215)
- 914 36 Outpatients/ (8472)
- 915 37 Outpatient Clinics, Hospital/ (14128)
- 916 38 (outpatient\$ or out-patient\$).tw. (111536)
- 917 39 Inpatients/ (12079)
- 918 40 (inpatient\$ or in-patient\$).tw. (1081478)
- 919 41 or/23-40 (4606154)
- 920 42 22 and 41 (76731)
- 921 43 exp "Referral and Consultation"/ (54863)

- 922 44 (refer or referr\$ or consult\$ or second opinion\$ or gatekeep\$).tw. (254611)
923 45 43 or 44 (279750)
924 46 42 and 45 (2627)
925 47 Ambulatory Care/ or ambulatory care facilities/ (46189)
926 48 Primary Health Care/ (52103)
927 49 exp General Practice/ (62966)
928 50 General Practitioners/ (1558)
929 51 Physicians, Family/ (14791)
930 52 Physicians, Primary Care/ (963)
931 53 gp\$.tw. (107669)
932 54 ((general or family) adj (practice\$ or practitioner\$ or physician\$ or doctor\$)).tw. (76526)
933 55 primary-care.tw. (63248)
934 56 ((primary or ambulatory) adj3 (care or health\$ or service\$ or center\$ or centre\$ or
935 practice\$)).tw. (95956)
936 57 Community Health Services/ (26382)
937 58 Community health nursing/ (18097)
938 59 ((walkin or walk-in or "walk in" or community health) adj3 (care or service\$ or centre\$ or
939 center\$ or clinic\$ or facilit\$)).tw. (4810)
940 60 or/47-59 (372571)
941 61 22 and 45 and 60 (543)
942 62 46 or 61 (2755)

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

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

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

949 Search Strategy:

950 -----

- 951 1 exp Gastroesophageal Reflux/ (21027)
952 2 exp Duodenogastric Reflux/ (1565)
953 3 (reflux\$ or gord or gerd or ger).tw. (39779)
954 4 exp Esophagitis/ (9302)
955 5 (esophagi\$ or oesophagi\$).tw. (11290)

- 956 6 exp Gastritis/ (17631)
957 7 (gastrit\$ or gastr\$ stas\$.tw. (16681)
958 8 or/1-7 (73538)
959 9 Proton Pump Inhibitors/ (3052)
960 10 Omeprazole/ (8882)
961 11 (ppi\$ or proton pump\$ or omeprazole\$ or losec\$ or rabeprazole\$ or pariet\$ or
962 pantoprazole\$ or protium\$ or lansoprazole\$ or zoton\$ or esomeprazole\$ or nexium\$ or
963 emozul\$.tw. (68843)

964 **Health economics studies on RQ 5 *H pylori***

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

- 968 1 sequen\$.tw. (780022)
969 2 tripl\$.tw. (57062)
970 3 quadrupl\$.tw. (6508)
971 4 ((standard\$ or convention\$) adj3 (therap\$ or treat\$ or regim\$)).tw. (72267)
972 5 or/1-4 (902378)
973 6 Proton Pump Inhibitors/ (2108)
974 7 Omeprazole/ (8195)
975 8 (ppi\$ or proton pump\$ or omeprazole\$ or losec\$ or rabeprazole\$ or pariet\$ or
976 pantoprazole\$ or protium\$ or lansoprazole\$ or zoton\$ or esomeprazole\$ or nexium\$).tw.
977 (63366)
978 9 or/6-8 (65253)
979 10 exp Nitroimidazoles/ (14387)
980 11 (nitroimidazole\$ or antiprotozoal\$ or metronidazole\$ or flagyl\$ or tinidazole\$ or
981 fasigyn\$.tw. (12981)
982 12 Clarithromycin/ (4696)
983 13 (clarithromycin\$ or klaracid\$.tw. (5782)
984 14 exp Amoxicillin/ (8484)
985 15 (amox\$ or amix\$ or amoram\$ or amoxidant\$ or alenamox\$ or rimoxallin\$.tw. (11714)
986 16 Bismuth/ (4343)
987 17 (bismuth\$ or tripotassium\$ or tri-potassium\$ or tri potassium\$ or de-noltab\$ or
988 denoltab\$ or de noltab\$.tw. (4148)
989 18 exp Tetracyclines/ (38179)
990 19 tetracyclin\$.tw. (25264)

- 991 20 exp Quinolones/ (31777)
- 992 21 (quinolon\$ or levofloxacin\$ or tavinic\$ or moxifloxacin\$ or avelox\$).tw. (13087)
- 993 22 or/10-21 (119449)
- 994 23 9 and 22 (3112)
- 995 24 5 or 23 (904002)
- 996 25 exp Helicobacter/ (27822)
- 997 26 Helicobacter Infections/ (23064)
- 998 27 exp Campylobacter/ (9027)
- 999 28 (helicobac\$ or campylobact\$ or pylori\$).tw. (47975)
- 1000 29 or/25-28 (50973)
- 1001 30 24 and 29 (7159)

1002 **Health economics searches on review Question 6 - Effectiveness of laparoscopic**
1003 **fundoplication compared to medical management in patients with GORD**

1004 The searches were undertaken in November 2011. Search filters to retrieve economic
1005 evaluations and quality of life papers were appended to the following search strategy to
1006 identify relevant evidence

1007 Database: Ovid MEDLINE(R) <1948 to November Week 3 2011>

1008 -----

- 1009 1 exp Gastroesophageal Reflux/ (19796)
- 1010 2 exp Duodenogastric Reflux/ (1567)
- 1011 3 (reflux\$ or gord or gerd or ger).tw. (37759)
- 1012 4 Esophageal Sphincter, Lower/ (466)
- 1013 5 lower esophageal sphincter.tw. (3192)
- 1014 6 lower oesophageal sphincter.tw. (893)
- 1015 7 (les or los).tw. (15977)
- 1016 8 Heartburn/ (1461)
- 1017 9 heartburn\$.tw. (3294)
- 1018 10 pyros\$.tw. (2439)
- 1019 11 acid exposure.tw. (1801)
- 1020 12 Dyspepsia/ (6800)
- 1021 13 (dyspep\$ or indigestion\$).tw. (9598)
- 1022 14 (regurg\$ or waterbrash\$).tw. (23945)
- 1023 15 exp Esophagitis/ (8866)

- 1024 16 (esophagi\$ or oesophagi\$.tw. (10675)
- 1025 17 exp Gastritis/ (17444)
- 1026 18 (gastrit\$ or gastr\$ stas\$.tw. (16251)
- 1027 19 or/1-18 (120456)
- 1028 20 Fundoplication/ (3123)
- 1029 21 fundoplicat\$.tw. (3941)
- 1030 22 gastroplicat\$.tw. (50)
- 1031 23 nissen.tw. (2208)
- 1032 24 (toupet or lind or watson or besley or hill).tw. (15508)
- 1033 25 (antireflux\$ or anti-reflux\$ or anti reflux\$.tw. (4362)
- 1034 26 or/20-25 (22949)
- 1035 27 19 and 26 (6329)

1036 **Health economics searches on review Question 7 – other medical or surgical**
1037 **treatments for GORD/dyspepsia**

1038 The searches were undertaken in July 2013. Search filters to retrieve economic evaluations
1039 and quality of life papers were appended to the following search strategy to identify relevant
1040 evidence

1041 Database: Ovid MEDLINE(R) <1946 to June Week 4 2013>

1042 Search Strategy:

1043 -----

- 1044 1 exp Gastroesophageal Reflux/ (21834)
- 1045 2 exp Duodenogastric Reflux/ (1598)
- 1046 3 (reflux\$ or gord or gerd or ger).tw. (41116)
- 1047 4 Esophageal Sphincter, Lower/ (636)
- 1048 5 lower esophageal sphincter.tw. (3396)
- 1049 6 lower oesophageal sphincter.tw. (951)
- 1050 7 (les or los).tw. (18554)
- 1051 8 Heartburn/ (1711)
- 1052 9 heartburn\$.tw. (3837)
- 1053 10 pyros\$.tw. (4848)
- 1054 11 acid exposure.tw. (2136)
- 1055 12 Dyspepsia/ (7239)
- 1056 13 (dyspep\$ or indigestion\$.tw. (10520)

- 1057 14 (regurg\$ or waterbrash\$).tw. (25940)
- 1058 15 exp Esophagitis/ (9626)
- 1059 16 (esophagi\$ or oesophagi\$).tw. (11821)
- 1060 17 exp Gastritis/ (18039)
- 1061 18 (gastrit\$ or gastr\$ stas\$).tw. (17309)
- 1062 19 exp Abdominal Pain/ (25169)
- 1063 20 ((abdom\$ or stomach\$) adj3 (ache\$ or pain\$ or discomfort\$)).tw. (38261)
- 1064 21 or/1-20 (184907)
- 1065 22 Proton Pump Inhibitors/ (3452)
- 1066 23 Omeprazole/ (9602)
- 1067 24 (ppi\$ or proton pump\$ or omeprazole\$ or losec\$ or rabeprazole\$ or pariet\$ or
1068 pantoprazole\$ or protium\$ or lansoprazole\$ or zoton\$ or esomeprazole\$ or nexium\$ or
1069 emozul\$).tw. (73807)
- 1070 25 or/22-24 (75976)
- 1071 26 (nocturn\$ or night\$ or evening\$ or bed\$ or sleep\$).tw. (265507)
- 1072 27 ((split\$ or separat\$ or divi\$ or even\$ or spread\$ or multipl\$ or alter\$ or chang\$ or
1073 reduc\$ or less\$ or small\$ or low\$) adj3 dos\$).tw. (212809)
- 1074 28 25 and (26 or 27) (3312)
- 1075 29 21 and 28 (952)
- 1076 30 exp Histamine H2 Antagonists/ (18438)
- 1077 31 (h2ra\$ or h2-ra\$ or "h2 ra\$").tw. (456)
- 1078 32 (histamin\$ adj3 (antagon\$ or block\$ or recep\$)).tw. (11644)
- 1079 33 (h2\$ adj3 (antagon\$ or hist\$ or block\$ or recep\$)).tw. (15499)
- 1080 34 cimetidin\$.tw. (10324)
- 1081 35 tagamet.tw. (97)
- 1082 36 ranitidin\$.tw. (5605)
- 1083 37 zantac.tw. (58)
- 1084 38 famotidin\$.tw. (1728)
- 1085 39 nizatidin\$.tw. (375)
- 1086 40 axid.tw. (11)
- 1087 41 or/30-40 (36871)
- 1088 42 25 and 41 (4294)
- 1089 43 21 and 42 (1658)

- 1090 44 Dopamine Antagonists/ (9777)
1091 45 (dopamin\$ adj3 (receptor\$ or antagonist\$)).tw. (29089)
1092 46 prokinetic\$.tw. (2029)
1093 47 Metoclopramide/ (4516)
1094 48 (metoclopramide or maxolon).tw. (5018)
1095 49 Domperidone/ (1556)
1096 50 (domperidone or motilium).tw. (1883)
1097 51 (itopride or ganaton).tw. (73)
1098 52 (mosapride or biononus).tw. (211)
1099 53 or/44-52 (41139)
1100 54 21 and 53 (1541)
1101 55 exp Laparoscopy/ (66357)
1102 56 laparoscopes/ (3399)
1103 57 surgical procedures, Minimally Invasive/ (16403)
1104 58 (laparoscop\$ or celioscop\$ or keyhole\$).tw. (77671)
1105 59 or/55-58 (101549)
1106 60 Fundoplication/ (3485)
1107 61 fundoplicat\$.tw. (4270)
1108 62 gastroplicat\$.tw. (51)
1109 63 nissen.tw. (2360)
1110 64 (toupet or lind or watson or besley or hill).tw. (17231)
1111 65 (antireflux\$ or anti-reflux\$ or anti reflux\$).tw. (4603)
1112 66 or/60-65 (25195)
1113 67 59 and 66 (3160)
1114 68 21 and 67 (2451)
1115 69 29 or 43 or 54 or 68 (6046)

1116 **Health economics studies for RQ8 on Barrett's oesophagus surveillance**
1117 The searches were undertaken in June 2012. Search filters to retrieve economic evaluations
1118 and quality of life papers were appended to the following search strategy to identify relevant
1119 evidence.

1120
1121 Database: Ovid MEDLINE(R) <1946 to June Week 3 2012>

1122 Search Strategy:

1123 -----

- 1124 1 Barrett Esophagus/ (5540)
- 1125 2 barrett\$.tw. (6502)
- 1126 3 ((column\$ or speciali\$ or intestinali\$) adj3 (epithel\$ or oesophag\$ or esophag\$ or
1127 mucos\$)).tw. (4150)
- 1128 4 ((metaplas\$ or dysplasi\$ or neoplasia\$) adj3 (column\$ or intestin\$ or epithel\$ or
1129 oesophag\$ or esophag\$ or mucos\$ or high-grade\$ or low-grade\$)).tw. (13889)
- 1130 5 or/1-4 (21677)
- 1131 6 exp Mass Screening/ (91380)
- 1132 7 exp Population Surveillance/ (44528)
- 1133 8 (screen\$ or surveillan\$ or monitor\$).tw. (850390)
- 1134 9 or/6-8 (903995)
- 1135 10 exp Endoscopy/ (232503)
- 1136 11 endoscop\$.tw. (117555)
- 1137 12 chromoendoscop\$.tw. (493)
- 1138 13 (esophagoscop\$ or oesophagoscop\$).tw. (1734)
- 1139 14 exp Biopsy/ (206772)
- 1140 15 biops\$.tw. (253125)
- 1141 16 or/10-15 (607756)
- 1142 17 9 and 16 (43821)
- 1143 18 5 and 17 (2236)

1144

1145 **Health economics update search**

1146 A broad update search was conducted in November and December 2013.

1147

1148 Database: Ovid MEDLINE(R) <1946 to November Week 3 2013>

1149 Search Strategy:

1150 -----

- 1151 1 Dyspepsia/ (7350)
- 1152 2 (dyspep\$ or indigestion\$).tw. (10747)
- 1153 3 (regurg\$ or waterbrash\$).tw. (26570)
- 1154 4 Heartburn/ (1741)

- 1155 5 heartburn\$.tw. (3927)
- 1156 6 pyros\$.tw. (5409)
- 1157 7 acid exposure.tw. (2187)
- 1158 8 exp Peptic Ulcer/ (72959)
- 1159 9 ((peptic\$ or gastr\$ or duoden\$ or stomach\$) adj3 ulcer\$.tw. (53892)
- 1160 10 exp Esophagitis/ (9796)
- 1161 11 (esophagi\$ or oesophagi\$.tw. (12055)
- 1162 12 exp Gastritis/ (18238)
- 1163 13 (gastrit\$ or gastr\$ stas\$.tw. (17592)
- 1164 14 exp Gastroesophageal Reflux/ (22243)
- 1165 15 exp Duodenogastric Reflux/ (1603)
- 1166 16 (reflux\$ or gord or gerd or ger).tw. (41924)
- 1167 17 Esophageal Sphincter, Lower/ (671)
- 1168 18 lower esophageal sphincter.tw. (3442)
- 1169 19 lower oesophageal sphincter.tw. (960)
- 1170 20 (les or los).tw. (19218)
- 1171 21 or/1-20 (204562)
- 1172 22 exp Gastrointestinal Neoplasms/ (290193)
- 1173 23 ((stomach\$ or oesoph\$ or esoph\$ or intestin\$ or gastric\$) adj3 (cancer\$ or carcinoma\$
1174 or adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (95901)
- 1175 24 ((upper digestive\$ or upper gastr\$ or upper gi) adj3 (cancer\$ or carcinoma\$ or
1176 adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (1544)
- 1177 25 or/22-24 (305698)
- 1178 26 21 or 25 (487765)
- 1179 27 "Value of Life"/ (5495)
- 1180 28 Quality-Adjusted Life Years/ (7347)
- 1181 29 quality adjusted life.tw. (6165)
- 1182 30 (qaly\$ or qald\$ or qale\$ or qtime\$.tw. (5151)
- 1183 31 disability adjusted life.tw. (1204)
- 1184 32 daly\$.tw. (1179)
- 1185 33 Health Status Indicators/ (21035)
- 1186 34 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform
1187 thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15680)

- 1188 35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form
1189 six).tw. (1085)
- 1190 36 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform
1191 twelve or short form twelve).tw. (2653)
- 1192 37 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform
1193 sixteen or short form sixteen).tw. (20)
- 1194 38 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform
1195 twenty or short form twenty).tw. (334)
- 1196 39 (euroqol or euro qol or eq5d or eq 5d).tw. (3796)
- 1197 40 (hye or hyes).tw. (53)
- 1198 41 health\$ year\$ equivalent\$.tw. (37)
- 1199 42 (health adj3 state adj3 utilit\$.tw. (335)
- 1200 43 (utilit\$ adj3 (health\$ or valu\$ or weight\$ or scor\$ or measure\$)).tw. (5348)
- 1201 44 (hui or hui1 or hui2 or hui3).tw. (884)
- 1202 45 disutili\$.tw. (214)
- 1203 46 rosser.tw. (73)
- 1204 47 quality of wellbeing.tw. (6)
- 1205 48 quality of well-being.tw. (353)
- 1206 49 qwb.tw. (173)
- 1207 50 willingness to pay.tw. (2162)
- 1208 51 standard gamble\$.tw. (673)
- 1209 52 time trade off.tw. (741)
- 1210 53 time tradeoff.tw. (212)
- 1211 54 tto.tw. (585)
- 1212 55 (preferen\$ weight\$ or health state preferen\$).tw. (257)
- 1213 56 or/27-55 (62401)
- 1214 57 26 and 56 (1701)
- 1215 58 limit 57 to english language (1615)
- 1216 59 limit 58 to ed=20120201-20131204 (277)
- 1217
- 1218 Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 03,
1219 2013>
- 1220 Search Strategy:
- 1221 -----

- 1222 1 Dyspepsia/ (0)
1223 2 (dyspep\$ or indigestion\$).tw. (702)
1224 3 (regurg\$ or waterbrash\$).tw. (1426)
1225 4 Heartburn/ (0)
1226 5 heartburn\$.tw. (208)
1227 6 pyros\$.tw. (731)
1228 7 acid exposure.tw. (100)
1229 8 exp Peptic Ulcer/ (0)
1230 9 ((peptic\$ or gastr\$ or duoden\$ or stomach\$) adj3 ulcer\$).tw. (2009)
1231 10 exp Esophagitis/ (0)
1232 11 (esophagi\$ or oesophagi\$).tw. (588)
1233 12 exp Gastritis/ (0)
1234 13 (gastrit\$ or gastr\$ stas\$).tw. (665)
1235 14 exp Gastroesophageal Reflux/ (0)
1236 15 exp Duodenogastric Reflux/ (0)
1237 16 (reflux\$ or gord or gerd or ger).tw. (2733)
1238 17 Esophageal Sphincter, Lower/ (0)
1239 18 lower esophageal sphincter.tw. (129)
1240 19 lower oesophageal sphincter.tw. (17)
1241 20 (les or los).tw. (1831)
1242 21 or/1-20 (9799)
1243 22 exp Gastrointestinal Neoplasms/ (2)
1244 23 ((stomach\$ or oesoph\$ or esoph\$ or intestin\$ or gastric\$) adj3 (cancer\$ or carcinoma\$
1245 or adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (5670)
1246 24 ((upper digestive\$ or upper gastr\$ or upper gi) adj3 (cancer\$ or carcinoma\$ or
1247 adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (103)
1248 25 or/22-24 (5726)
1249 26 21 or 25 (14913)
1250 27 "Value of Life"/ (0)
1251 28 Quality-Adjusted Life Years/ (0)
1252 29 quality adjusted life.tw. (574)
1253 30 (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (469)
1254 31 disability adjusted life.tw. (153)

- 1255 32 daly\$.tw. (140)
- 1256 33 Health Status Indicators/ (0)
- 1257 34 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform
1258 thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (1204)
- 1259 35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form
1260 six).tw. (373)
- 1261 36 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform
1262 twelve or short form twelve).tw. (305)
- 1263 37 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform
1264 sixteen or short form sixteen).tw. (3)
- 1265 38 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform
1266 twenty or short form twenty).tw. (11)
- 1267 39 (euroqol or euro qol or eq5d or eq 5d).tw. (449)
- 1268 40 (hye or hyes).tw. (2)
- 1269 41 health\$ year\$ equivalent\$.tw. (2)
- 1270 42 (health adj3 state adj3 utilit\$).tw. (41)
- 1271 43 (utilit\$ adj3 (health\$ or valu\$ or weight\$ or scor\$ or measure\$)).tw. (450)
- 1272 44 (hui or hui1 or hui2 or hui3).tw. (82)
- 1273 45 disutili\$.tw. (22)
- 1274 46 rosser.tw. (1)
- 1275 47 quality of wellbeing.tw. (2)
- 1276 48 quality of well-being.tw. (9)
- 1277 49 qwb.tw. (5)
- 1278 50 willingness to pay.tw. (234)
- 1279 51 standard gamble\$.tw. (31)
- 1280 52 time trade off.tw. (57)
- 1281 53 time tradeoff.tw. (7)
- 1282 54 tto.tw. (55)
- 1283 55 (preferen\$ weight\$ or health state preferen\$).tw. (23)
- 1284 56 or/27-55 (3571)
- 1285 57 26 and 56 (64)
- 1286 58 limit 57 to english language (60)
- 1287
- 1288 Database: Embase <1980 to 2013 Week 48>

1289 Search Strategy:

1290 -----

- 1291 1 dyspepsia/ (24578)
- 1292 2 (dyspep\$ or indigestion\$).tw. (15222)
- 1293 3 indigestion/ (1623)
- 1294 4 (regurg\$ or waterbrash\$).tw. (37061)
- 1295 5 heartburn/ (9009)
- 1296 6 heartburn\$.tw. (5633)
- 1297 7 pyros\$.tw. (7133)
- 1298 8 acid exposure.tw. (2969)
- 1299 9 exp peptic ulcer/ (99843)
- 1300 10 ((peptic\$ or gastr\$ or duoden\$ or stomach\$) adj3 ulcer\$).tw. (63195)
- 1301 11 exp esophagitis/ (23422)
- 1302 12 (esophagi\$ or oesophagi\$).tw. (17107)
- 1303 13 exp gastritis/ (50481)
- 1304 14 (gastrit\$ or gastr\$ stas\$).tw. (22739)
- 1305 15 exp gastroesophageal reflux/ (43044)
- 1306 16 exp duodenogastric reflux/ (2508)
- 1307 17 laryngopharyngeal reflux/ (814)
- 1308 18 (reflux\$ or gord or gerd or ger).tw. (59125)
- 1309 19 lower esophagus sphincter/ (9546)
- 1310 20 lower esophageal sphincter.tw. (4406)
- 1311 21 lower oesophageal sphincter.tw. (1121)
- 1312 22 (les or los).tw. (40231)
- 1313 23 or/1-22 (333773)
- 1314 24 gastrointestinal tumor/ (9980)
- 1315 25 exp stomach cancer/ (63618)
- 1316 26 exp esophagus cancer/ (37040)
- 1317 27 exp intestine cancer/ (158216)
- 1318 28 ((stomach\$ or oesoph\$ or esoph\$ or intestin\$ or gastric\$) adj3 (cancer\$ or carcinoma\$
1319 or adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (124439)
- 1320 29 ((upper digestive\$ or upper gastr\$ or upper gi) adj3 (cancer\$ or carcinoma\$ or
1321 adenocarcinoma\$ or neoplasm\$ or tumor\$ or tumour\$ or malign\$)).tw. (2091)

1322	30	or/24-29 (300340)
1323	31	23 or 30 (605636)
1324	32	Quality Adjusted Life Year/ (11654)
1325	33	Short Form 36/ (10749)
1326	34	Health Status/ (82773)
1327	35	quality adjusted life.tw. (8411)
1328	36	(qaly\$ or qald\$ or qale\$ or qtime\$).tw. (8313)
1329	37	disability adjusted life.tw. (1479)
1330	38	daly\$.tw. (1569)
1331	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)
1333	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)
1335	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)
1337	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)
1339	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)
1341	44	(euroqol or euro qol or eq5d or eq 5d).tw. (6317)
1342	45	(hye or hyes).tw. (84)
1343	46	health\$ year\$ equivalent\$.tw. (43)
1344	47	(health adj3 state adj3 utilit\$).tw. (542)
1345	48	(utilit\$ adj3 (health\$ or valu\$ or weight\$ or scor\$ or measure\$)).tw. (7535)
1346	49	(hui or hui1 or hui2 or hui3).tw. (1206)
1347	50	disutili\$.tw. (351)
1348	51	rosser.tw. (88)
1349	52	quality of wellbeing.tw. (19)
1350	53	quality of well-being.tw. (372)
1351	54	qwb.tw. (192)
1352	55	willingness to pay.tw. (3188)
1353	56	standard gamble\$.tw. (770)
1354	57	time trade off.tw. (978)
1355	58	time tradeoff.tw. (224)

- 1356 59 tto.tw. (846)
- 1357 60 (preferen\$ weight\$ or health state preferen\$).tw. (371)
- 1358 61 or/32-60 (133769)
- 1359 62 31 and 61 (3878)
- 1360 63 limit 62 to embase (3493)
- 1361 64 limit 63 to (conference abstract or conference paper) (758)
- 1362 65 63 not 64 (2735)
- 1363 66 limit 65 to english language (2606)
- 1364 67 limit 66 to em=201201-201348 (522)
- 1365
- 1366 Database: Cochrane Library
- 1367 Search Name: ICG - Dyspepsia - Health Economics - Update Search 04 Dec 2013
- 1368 Date Run: 04/12/13 09:55:25.811
- 1369 Description: 04 Dec 2013
- 1370 ID SearchHits
- 1371 #1 MeSH descriptor: [Dyspepsia] this term only 867
- 1372 #2 dyspep* or indigestion*:ti,ab,kw 2360
- 1373 #3 regurg* or waterbrash*:ti,ab,kw 875
- 1374 #4 MeSH descriptor: [Heartburn] this term only 267
- 1375 #5 heartburn*:ti,ab,kw 982
- 1376 #6 pyros*:ti,ab,kw 93
- 1377 #7 acid exposure*:ti,ab,kw 1355
- 1378 #8 MeSH descriptor: [Peptic Ulcer] explode all trees 3601
- 1379 #9 (peptic* or gastr* or duoden* or stomach*) near ulcer*:ti,ab,kw 6634
- 1380 #10 MeSH descriptor: [Esophagitis] explode all trees 608
- 1381 #11 esophagi* or oesophagi*:ti,ab,kw 1356
- 1382 #12 MeSH descriptor: [Gastritis] explode all trees 514
- 1383 #13 gastrit* or gastr* stas*:ti,ab,kw 1355
- 1384 #14 MeSH descriptor: [Gastroesophageal Reflux] explode all trees 1387
- 1385 #15 MeSH descriptor: [Duodenogastric Reflux] explode all trees 52
- 1386 #16 reflux* or gord or gerd or ger:ti,ab,kw 3438
- 1387 #17 MeSH descriptor: [Esophageal Sphincter, Lower] this term only 35

1388	#18	lower esophageal sphincter:ti,ab,kw	504
1389	#19	lower oesophageal sphincter:ti,ab,kw	504
1390	#20	les or los:ti,ab,kw	2050
1391	#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	
1392		or #15 or #16 or #17 or #18 or #19 or #20	16791
1393	#22	MeSH descriptor: [Gastrointestinal Neoplasms] explode all trees	7424
1394	#23	(stomach* or oesoph* or esoph* or intestin* or gastric*) near (cancer* or carcinoma*	
1395		or adenocarcinoma* or neoplasm* or tumor* or tumour* or malign*):ti,ab,kw	
1396			4435
1397	#24	(upper digestive* or upper gastr* or upper gi) near (cancer* or carcinoma* or	
1398		adenocarcinoma* or neoplasm* or tumor* or tumour* or malign*):ti,ab,kw	115
1399	#25	#22 or #23 or #24	9400
1400	#26	#21 or #25 from 2012 to 2013	1078
1401			
1402		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 œacid exposureœ or esophagi* or oesophagi* or gastrit* or gastr* or stas* or reflux* or gord or gerd or ger or œlower esophageal sphincterœ 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
1403			
1404		HEED	
1405	1	dyspep* or indigestion* or regurg* or waterbrash or heartburn or pyros* or gastrit* or acid*	
1406		or gastr* or stas* or reflux* or gord or gerd or ger or les or los	
1407		AND	
1408	2	qaly* or qald* or qale* or qtime* or quality or valu* or weight* or scor* or measure	
1409			

1410

1411 **Notes:**

1412 PubMed – only limited by date, adding the publisher limit retrieved too many results (not
1413 necessarily recent).

1414 HEED – Line 1: Exported new articles (2012 – 2013). Lines 1 AND 2: exported records from
1415 2012 – 2013

1416

1417 **Health economics filters**

1418 The MEDLINE economic evaluations and quality of life search filters are presented below.
1419 They were translated for use in the MEDLINE In-Process and Embase databases.

1420 **Specific economic evaluations filter**

1421 1 "Value of Life"/ (5218)

1422 2 Quality-Adjusted Life Years/ (5682)

1423 3 quality adjusted life.tw. (4551)

1424 4 (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (3807)

1425 5 disability adjusted life.tw. (870)

1426 6 daly\$.tw. (882)

1427 7 Health Status Indicators/ (17920)

1428 8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform
1429 thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
1430 (12459)

1431 9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short
1432 form six).tw. (898)

1433 10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform
1434 twelve or short form twelve).tw. (1936)

1435 11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform
1436 sixteen or short form sixteen).tw. (18)

1437 12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform
1438 twenty or short form twenty).tw. (308)

1439 13 (euroqol or euro qol or eq5d or eq 5d).tw. (2690)

1440 14 (hye or hyes).tw. (52)

1441 15 health\$ year\$ equivalent\$.tw. (36)

1442 16 (health adj3 state adj3 utilit\$).tw. (232)

1443 17 (utilit\$ adj3 (health\$ or valu\$ or weight\$ or scor\$ or measure\$)).tw. (4170)

1444 18 (hui or hui1 or hui2 or hui3).tw. (698)

- 1445 19 disutili\$.tw. (168)
- 1446 20 rosser.tw. (72)
- 1447 21 quality of wellbeing.tw. (5)
- 1448 22 quality of well-being.tw. (297)
- 1449 23 qwb.tw. (150)
- 1450 24 willingness to pay.tw. (1659)
- 1451 25 standard gamble\$.tw. (578)
- 1452 26 time trade off.tw. (600)
- 1453 27 time tradeoff.tw. (190)
- 1454 28 tto.tw. (456)
- 1455 29 (preferen\$ weight\$ or health state preferen\$).tw. (209)
- 1456 30 Or/1-29

1457 **Economic evaluations**

- 1458 1 Economics/
- 1459 2 exp "Costs and Cost Analysis"/
- 1460 3 Economics, Dental/
- 1461 4 exp Economics, Hospital/
- 1462 5 exp Economics, Medical/
- 1463 6 Economics, Nursing/
- 1464 7 Economics, Pharmaceutical/
- 1465 8 Budgets/
- 1466 9 exp Models, Economic/
- 1467 10 Markov Chains/
- 1468 11 Monte Carlo Method/
- 1469 12 Decision Trees/
- 1470 13 econom\$.tw.
- 1471 14 cba.tw.
- 1472 15 cea.tw.
- 1473 16 cua.tw.
- 1474 17 markov\$.tw.
- 1475 18 (monte adj carlo).tw.
- 1476 19 (decision adj2 (tree\$ or analys\$)).tw.

- 1477 20 (cost or costs or costing\$ or costly or costed).tw.
- 1478 21 (price\$ or pricing\$).tw.
- 1479 22 budget\$.tw.
- 1480 23 expenditure\$.tw.
- 1481 24 (value adj2 (money or monetary)).tw.
- 1482 25 (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw.
- 1483 26 or/1-25
- 1484 **Quality of life**
- 1485 1 "Value of Life"/
- 1486 2 Quality-Adjusted Life Years/
- 1487 3 quality adjusted life.tw.
- 1488 4 (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
- 1489 5 disability adjusted life.tw.
- 1490 6 daly\$.tw.
- 1491 7 Health Status Indicators/
- 1492 8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform
 1493 thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
- 1494 9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short
 1495 form six).tw.
- 1496 10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform
 1497 twelve or short form twelve).tw.
- 1498 11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform
 1499 sixteen or short form sixteen).tw.
- 1500 12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform
 1501 twenty or short form twenty).tw.
- 1502 13 (euroqol or euro qol or eq5d or eq 5d).tw.
- 1503 14 (hye or hyes).tw.
- 1504 15 health\$ year\$ equivalent\$.tw.
- 1505 16 (health adj3 state adj3 utilit\$).tw.
- 1506 17 (utilit\$ adj3 (health\$ or valu\$ or weight\$ or scor\$ or measure\$)).tw.
- 1507 18 (hui or hui1 or hui2 or hui3).tw.
- 1508 19 disutili\$.tw.
- 1509 20 rosser.tw.
- 1510 21 quality of wellbeing.tw.

1511	22	quality of well-being.tw.
1512	23	qwb.tw.
1513	24	willingness to pay.tw.
1514	25	standard gamble\$.tw.
1515	26	time trade off.tw.
1516	27	time tradeoff.tw.
1517	28	tto.tw.
1518	29	(preferen\$ weight\$ or health state preferen\$).tw.
1519	30	or/1-30
1520		

1520 **C.3 Summary of the modified GRADE approach**

1522 For the review questions [2014 update]:

1523 Review question 1: When should (and with what indications) patients with uninvestigated
1524 dyspepsia be referred for endoscopy for further investigation and review of treatment plan?

1525 Review question 2: Which risk factors indicate endoscopy in order to exclude Barrett's
1526 oesophagus?

1527 Review question 3: Which patient characteristics/clinical indicators/criteria indicate referral of
1528 a patient with dyspepsia, heartburn, or confirmed GORD managed in primary care to a
1529 consultant led medical or surgical service (specialist services)?

1530 For the above three review questions [2014 update], a modified-GRADE approach was used
1531 for critical appraisal and evidence synthesis to aid decision making. The criteria used in the
1532 modified-GRADE approach were adapted from the Hayden et al. (2006) QUIPS checklist for
1533 prognostic study (link for the Guideline Manual 2012).

1534 The methodology of the modified-GRADE approach was as follow:

1535 Quality appraisal using modified-GRADE approach

1536 The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a
1537 common, sensible and transparent approach to grading quality of evidence which was
1538 developed by experts internationally. Over 70 international guidance developing
1539 organisations have endorsed the use of GRADE, including NICE, SIGN, NHS Quality
1540 Improvement Scotland, Cochrane Collaboration, WHO, BMJ Clinical Evidence, Agency for
1541 Healthcare Research and Quality (AHRQ) and many others.

1542 GRADE was originally developed for grading quality of intervention and diagnostic accuracy
1543 study only. However, for the purpose of this particular review question on risk factors, the
1544 GRADE criteria were modified and adapted by using the Hayden et al. (2006) checklist for
1545 prognostic study (NICE Guideline Manual, 2012). The modified-GRADE criteria were used to
1546 appraise the quality of individual studies, as well as the quality of individual risk factors
1547 across different studies. The rationales for downgrading the evidence based on the five
1548 modified-GRADE criteria were explicitly reported using 'footnote' for each modified-GRADE
1549 profile.

1550 Summary of the modified-GRADE approach:

1551 Section 1: Outcome vs individual study, and meta-analysis

1552 In GRADE approach for intervention question, the quality of evidence on each outcome is
 1553 assessed according to the impact of the risk of bias from the study to that particular outcome.
 1554 If there is more than one study that reported such outcome, the overall judgement of the
 1555 quality for that outcome across different studies will be made.

1556 This is because in the same intervention study (e.g. RCT), there may be different levels or
 1557 magnitude of the impact of the risk of bias on different outcomes measured in the same
 1558 study. For example, in a single-blinded RCT (assessor-blinded only) on antibiotics for
 1559 infected wound, the risk of bias for patient-reported pain of the wound (outcome 1) would be
 1560 different compared to bacteria eradication rate (based on histology) (outcome 2) due to the
 1561 single-blinded design of the study.

1562 In prognostic study (or clinical prediction model), these varying degrees of risk of bias in a
 1563 study do not apply same as in an intervention study. This is because in a multivariate
 1564 regression model (MRM), the sources of the risk of bias commonly came from how the data
 1565 of the individual risk factors or predictors was collected as a whole in a study, and what kinds
 1566 of adjustment were made in the MRM regarding baseline confounders and covariates.
 1567 Hence, the risk of bias in a study would have impacted the MRM as whole (i.e. all risk factors
 1568 or predictors entered in the MRM equally). Therefore, the quality of an individual study would
 1569 apply across to all risk factors or predictors in that particular individual study.

1570 Due to the varying methods used in different studies (e.g. different multivariate regression
 1571 models in different studies used different dependent variables as risk factors or predictors,
 1572 used different covariates, adjusted for different confounding factors), in other words, there
 1573 are no two exactly identical multivariate regression models that could be pooled in its
 1574 entirety. The only approach to conduct meta-analysis is to obtain IPD data from each study
 1575 and then re-run a single MRM using all the IPD data from all included studies. This would be
 1576 outside the development timeframe of this guideline.

1577 Therefore, no meta-analysis was conducted to combine individual risk factors or predictors
 1578 across different MRMs in different studies. Nevertheless, if there are more than one included
 1579 studies for a particular risk factor or predictor, the evidence would be presented based on
 1580 individual risk factors or predictors across different studies to aid discussion and decision
 1581 making. Otherwise, the evidence would be presented as individual studies.

1582 Section 2: Criteria and downgrading

1583 There are four quality categories in GRADE, namely 'High', 'Moderate', 'Low' and 'Very low'.
 1584 For prognostic study (or clinical prediction model), case control or cross-sectional study was
 1585 considered as appropriate study designs and hence under the modified-GRADE approach,
 1586 these two study designs would start from 'High' quality (or high 'confidence' in the effect
 1587 estimates). Then the evidence would be downgraded based on the following modified
 1588 framework:

1589

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	<ol style="list-style-type: none"> 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. 	<p>i) Downgrade 1 level if either (1) or (2) or (3) were not satisfied.</p> <p>ii) Downgrade 2 levels if more than 2 criteria were not satisfied.</p> <p>If there are more than one included studies, downgrade 1 level if >50% of the included studies been downgraded due to i).</p> <p>If there are more than one included studies, downgrade 2 levels if >50% of the included studies been downgraded due to ii).</p>
Inconsistency	<ol style="list-style-type: none"> 1) Same direction of effect estimates across all different studies. 2) Overlaps of 95%CI. 	<p>Downgrade 1 level if either (1) or (2) or both were not satisfied.</p> <p>Note: this criterion is not applicable to single study.</p>
Imprecision	<p>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):</p> <ol style="list-style-type: none"> 1) Model diagnostics: Assumption of normality (1a); Multicollinearity (1b); Goodness-of-fit (1c). 2) Reproducibility (validation) . 	<p>i) Downgrade 1 level if either (1) or (2) was not satisfied.</p> <p>ii) Downgrade 2 levels if both (1) and (2) were not satisfied.</p> <p>If there are more than one included studies, downgrade 2 levels if >50% of the included studies been downgraded due to i) or ii).</p>
Other considerations	<ol style="list-style-type: none"> 1) Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. 	<p>Downgrade 1 level if (1) was not satisfied.</p> <p>If there are more than one included studies, downgrade 1 level if >50% of the included studies been downgraded.</p>

- 1590 For the quality appraisal for individual studies for review question 2, please see below. For
1591 the full modified-GRADE profiles, please also see appendix F.
- 1592 [Note: For review question 1, since only 2 studies were included and hence the 2 individual
1593 studies were discussed in the Full guideline chapter; for review question 3, no study
1594 identified that met the inclusion criteria].
- 1595 Table below shows review question 2: Quality appraisal of individual studies – Modified
1596 GRADE – Criteria adapted from the Hayden et al (2006) checklist.
- 1597

	<p>•Prospective (1)</p> <p>•Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. (2)*</p> <p><u>Note*: To adjust potential confounders that are not part of the independent variables (risk factors) being studied.</u></p>	<p>•The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. (1)</p> <p>•The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. (2)</p> <p>•The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. (3)</p>	<p>•Same direction of effect estimates across different studies. (1)</p> <p>•Overlaps of 95%CI (2)</p>	<p>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):</p> <p>•Model diagnostics: Assumption of normality (1a); Multicollinearity (1b); Goodness-of-fit (1c).</p> <p>•Reproducibility (validation) (2)</p>	<p>•Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. (1)</p>	
	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

