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

C.1 Review protocols

Table 1: Review question 1

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td><strong>Status</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Intervention/indications</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
- 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.
<table>
<thead>
<tr>
<th>Control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No endoscopy</td>
<td>• Heath related QOL (using disease specific tools)</td>
</tr>
<tr>
<td>• Delayed endoscopy</td>
<td>• Resolution of symptoms (Critical?)</td>
</tr>
<tr>
<td></td>
<td>• Adverse events (Bleeding, oesophageal perforation, pneumothorax, anxiety)</td>
</tr>
<tr>
<td></td>
<td>• Mortality</td>
</tr>
<tr>
<td></td>
<td>• Medication use – frequency/dose</td>
</tr>
<tr>
<td></td>
<td>• GP / hospital visits (resource use)</td>
</tr>
<tr>
<td></td>
<td>• Change to diagnosis and subsequent management (Critical).</td>
</tr>
<tr>
<td></td>
<td>• New diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Patient satisfaction/preferences</td>
</tr>
</tbody>
</table>

**Other criteria for inclusion/exclusion of studies**

**Include**

- Patients with newly onset signs/symptoms
- Primary care setting or patients referred to secondary care for endoscopy

**Exclude**

- Patients with previous Endoscopy within 1 year
- Non English Language studies
- Abstract only studies.

**Search strategies**

No restriction but exclude case series, case reports and qualitative studies.

**Review strategies**

- The NICE methodology checklist for intervention or prognostic studies will be used as a guide to appraise the quality of individual studies
- Data on all included studies will be extracted into evidence tables
- Where statistically possible, a meta-analytical approach will be used to give an overall summary effect
- All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements.

**Identified key background studies**


**Table 2: Review question 2**

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
</table>

National Institute for Health and Care Excellence 2014.
### 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
Adults (18 years and older)

**Include**
- Histological confirmed Barrett’s oesophagus
- Metaplasia/specialised intestinal metaplasia
- Dyplasia (high and low grade)
- Columnar epithelium

**Exclude**
- 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
**Include**
- 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’
<table>
<thead>
<tr>
<th><strong>Dyspepsia and gastro-oesophageal reflux disease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Review protocols_searches_summary of modified GRADE</td>
</tr>
</tbody>
</table>

- Previous / Paediatric reflux surgery

**Exclude**
- 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
### Dyspepsia and gastro-oesophageal reflux disease

Review protocols_searches_summary of modified GRADE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Proportion with positive diagnosis of Barrett’s oesophagus</td>
<td></td>
</tr>
<tr>
<td>• Size/length of Barrett’s oesophagus.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other criteria for inclusion/exclusion of studies</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Studies that report outcomes in multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>• Prospective studies</td>
<td></td>
</tr>
<tr>
<td>(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).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other criteria for inclusion/exclusion of studies</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Studies analyzed using univariate analysis only</td>
<td></td>
</tr>
<tr>
<td>• Prevalence studies for existing carcinoma</td>
<td></td>
</tr>
<tr>
<td>• Studies reporting outcomes of treatment for Barrett's oesophagus</td>
<td></td>
</tr>
<tr>
<td>• Surveillance of patients with Barrett’s oesophagus for progression</td>
<td></td>
</tr>
<tr>
<td>• Population screening studies.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Search strategies</th>
<th>Systematic reviews and primary prognostic studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review strategies</td>
<td>Study quality will be evaluated using the NICE prognostic checklist</td>
</tr>
<tr>
<td>• Data on all included studies will be extracted into evidence tables</td>
<td></td>
</tr>
<tr>
<td>• Where statistically possible, a meta-analytical approach will be used</td>
<td></td>
</tr>
<tr>
<td>• to give an overall summary effect</td>
<td></td>
</tr>
<tr>
<td>• All key outcomes from evidence will be presented in GRADE profiles or</td>
<td></td>
</tr>
<tr>
<td>• modified profiles and further summarized in evidence statements.</td>
<td></td>
</tr>
</tbody>
</table>

|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

National Institute for Health and Care Excellence 2014.
Table 3: Review question 3

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td><strong>Status</strong></td>
</tr>
</tbody>
</table>

### Population

**Include**
- GORD/GERD
- Dyspepsia (investigated/uninvestigated dyspepsia, non-ulcer dyspepsia, functional dyspepsia)
- Peptic ulcer disease
- Heartburn
- Reflux

(*populations covered – based on CG17 plus functional dyspepsia)

**PLUS other search terms**
- New onset symptoms (while on medication)
- Persistent symptoms > 1 month
- Refractory
- Symptomatic
- Treatment failure
- Long term self-care > 10 years
- Failed on trial of PPI and *H pylori* test and treat.

**Intervention/indications**

Include (search terms)
- Specialist
- Consultant
- Gastroenterologist
<table>
<thead>
<tr>
<th>Control</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escape</td>
<td></td>
</tr>
<tr>
<td>Referral</td>
<td></td>
</tr>
<tr>
<td>Expert</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
</tbody>
</table>

Exclude
- Primary care
- GP
- Endoscopy.
### Dyspepsia and gastro-oesophageal reflux disease

Review protocols_searches_summary of modified GRADE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Health related QOL</td>
</tr>
<tr>
<td></td>
<td>• Resolution/improvement of Symptoms / VAS</td>
</tr>
<tr>
<td></td>
<td>• Patient satisfaction</td>
</tr>
<tr>
<td></td>
<td><strong>Important</strong></td>
</tr>
<tr>
<td></td>
<td>• Medication use/dose</td>
</tr>
<tr>
<td></td>
<td>• GP/Hospital visits</td>
</tr>
<tr>
<td></td>
<td>• Heartburn (% of days free).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other criteria for inclusion/exclusion of studies</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Any study illustrates ‘who’ (patient characteristic, clinical indicators, criteria) should be managed outside primary care that resulted in better patient outcomes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other criteria for inclusion/exclusion of studies</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Studies where the healthcare structure is considerably different to the UK where upwards referral for specialist treatment is not comparable.</td>
</tr>
</tbody>
</table>

| Search strategies | No restriction on study design (but will exclude case series, case reports, narrative review and qualitative study). |

<table>
<thead>
<tr>
<th>Review strategies</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Data on all included studies will be extracted into evidence tables</td>
</tr>
<tr>
<td></td>
<td>• All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements</td>
</tr>
<tr>
<td></td>
<td>• Narrative/qualitative synthesis of evidence may be required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identified key background studies</th>
<th>Systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None indentified</td>
</tr>
</tbody>
</table>

|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
### 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. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>To compare different PPIs to see which is the most effective to reduce symptoms and reflux exposure.</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>English only.</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Systematic reviews/meta-analysis, RCTs (blind or open-label).</td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td>Published papers (full text only).</td>
<td></td>
</tr>
</tbody>
</table>
| 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  
  Include  
  • Los Angeles classification grade C or D, Savary-Miller grade 3 or 4  
  Exclude  
  • 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  
  Include  
  • Omeprazole  
  • Rabeprazole (sodium)  
  • Lansoprazole  
  • Esomeprazole  
  • Pantoprazole  
  Exclude  
  • Dexlansoprazole – not licensed in UK  
  • H₂RAs (exclude from decision data set, but possibly use in comparison dataset in network analysis).  
  • |
| Control | • Placebo  
  • H₂RA  
  • Existing self-care  
  • (Each of the interventions listed in interventions box above will be |
### Outcomes

- Endoscopic appearance/chance in LA grade/resolution of oesophagitis (dichotomous)
- Health related QOL scales
- Acid exposure time (% time <pH4 on 24 hour monitoring)
- Progression to Barrett’s oesophagus or carcinoma
- Adverse events (headache, diarrhoea, nausea, drug interactions, metallic taste, rash)
- Mortality
- Hypergastro-anaemia.

### Other criteria for inclusion/exclusion of studies

#### Include

- Studies comparing the above listed treatment regimens
- >30-days follow-up period

#### Exclude

- Non-randomised studies, observational studies; and studies not published full-text (i.e. conference abstracts); or systematic reviews that contain any of these types of studies
- Studies with mixed populations (i.e. some patients within the study population who are not grade C or D) will only be included if outcomes are clearly separated for these groups
- <7 days regimens
- <30 day follow up
- Studies assessing pharmacological therapies other than, PPIs
- Studies using unlicensed drugs in both / all arms of the trial
- Dose ranging studies
- Studies which consider PPI plus alginate vs PPI alone.

### Search strategies

Systematic reviews/meta-analysis, RCTs, quasi-RCTs.

### Review strategies

- The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies
- Data on all included studies will be extracted into evidence tables
- Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis)
- All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements
- Sub group analyses will be undertaken for different dose and duration of treatment, and for populations with a definitive grade of oesophagitis C or D vs non definitive populations.

### Identified key background studies

Systematic reviews

### Table 5: Review question 5i

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question</strong></td>
<td>In patients with symptoms of dyspepsia who are positive for <em>Helicobacter pylori</em>, which eradication regimens are the most clinically effective in the eradication of <em>H pylori</em>?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To compare different regimens to see which is the most effective in the eradication of <em>H pylori</em>.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Systematic reviews/meta-analysis, RCTs (blind or open-label).</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published papers (full text only).</td>
</tr>
</tbody>
</table>
| **Population** | Adults (18 years and older) who have the following:  
- Symptoms of dyspepsia  
- Positive test for *H pylori*  
- Naive to previous antibiotic treatment  

**Include**  
- Uninvestigated dyspepsia  
- Ulcer dyspepsia (gastric or peptic)  
- Functional/non ulcer dyspepsia  

Can consider together for analysis – same risk associated with failure |
| **Exclude** | All subgroups (uninvestigated dyspepsia, ulcer dyspepsia, and functional dyspepsia) to be considered together.  

It may be possible to perform subgroup analysis on gastric and peptic ulcer separately if data allows  

Subgroup analysis will be performed, if possible, on intolerance. |
- Studies with patients with *H pylori* infection being treated for diagnosis other than dyspepsia - gastric cancer, NSAID related GI irritation, or population screening.
- Studies where *H pylori* has not been confirmed (i.e. studies in high prevalence areas where infection is assumed)
- Confirmed GORD
- Exclude studies conducted outside of Northern Europe or Germany, USA or Canada which included clarithromycin or levofloxacin as the intervention or comparator.
- Exclude studies conducted within Africa and Asia which included metronidazole as the intervention or comparator.

**Intervention/indications**

Comparison of the effectiveness of the following interventions – all compared to each other

A) SEQUENTIAL THERAPY
B) TRIPLE THERAPY
C) QUADRUPE THERAPY WITH BISMUTH
D) QUADRUPE THERAPY WITH THREE ANTIBIOTICS

We will include ‘Individual/named antibiotics’ in two classes (Penicillins and Macrolides) but assume a class effect in all others

**Include**
- Studies comparing different lengths of the above listed regimens
- Follow up period to be a minimum of one month after treatment

**Exclude**
- Regimens using two or more of the same class of antibiotics
- Quadruple with bismuth, 3 antibiotics, and no acid suppressant
- Quadruple with 2 antibiotics and 2 acid suppressants
- <7 days regimens.

**Control**

- Placebo
- Mono therapy
- Dual therapy
- Sequential/Triple/Quad therapy with H2RA as acid suppressant
- Triple therapy with no acid suppressant (with or without bismuth)
- Sequential/Triple/Quad therapy with off-label antibiotic included

Interventions listed here have been suggested to be the most relevant

The search will be based on the regimen/type used and for each names drug included

Assume all PPIs are equally effective when used within regimen for H Pylori eradication

License status of antibiotics for dyspepsia (one or more named drug per class is licensed for this indication)

- Macrolides ✓
- Quinolones (off label)
- Penicillins ✓
- Nitroimidazole ✓
- Tetracyclines ✓ indicated for GI infection
- Rifamycin (off label)
● Each of the interventions will be compared to one another also.
### Outcomes

<table>
<thead>
<tr>
<th>Critical</th>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication rate</td>
<td>Adherence to medication</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Mortality</td>
</tr>
<tr>
<td>Antibiotic resistance rates (if reported)</td>
<td>Health-related quality of life (using generic or disease-specific tools).</td>
</tr>
</tbody>
</table>

### Other criteria for inclusion/exclusion of studies

**Include**
- Studies with mixed populations (i.e. patients who have and have not tested positive for *H. pylori*) will only be included if outcomes are clearly separated between these groups.

**Exclude**
- 2nd line treatment (this will be covered in another question)
- Non-randomised studies, observational studies; and studies not published full-text (i.e. conference abstracts); or systematic reviews that contain any of these types of studies
- Mono or dual therapy (except for use in network meta-analysis)
- Regimens/therapies which include H2RA as acid suppressant (except as comparator dataset)
- Non-pharmacological therapies (i.e. herbal, probiotics)
- Studies assessing pharmacological therapies other than antibiotics, PPIs, H2RAs, chelates and complexes such as bismuth or sucralfate
- Studies using unlicensed drugs in all arms of the trial
- Studies using off-label drugs in all arms for 1st line
- Studies comparing the effectiveness of cytoprotective or mucolytic agents
- Quadruple therapy with 2 antibiotics and H2RAs (exclude for 1st line only).

### Search strategies

Systematic reviews/meta-analysis, RCTs, quasi-RCTs.

### Review strategies

The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies
Data on all included studies will be extracted into evidence tables
Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis)

We have assumed that:
- 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
- *H. pylori* eradication regimes using H2RAs are no longer used
<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Identified key background studies</th>
<th>Systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs (some included in reviews above)</td>
<td></td>
</tr>
</tbody>
</table>


**Table 6: Review question 5ii**

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question</strong></td>
<td>What <em>H pylori</em> eradication regimens should be offered as second-line treatments when first-line treatments fail?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To compare different regimens to see which is the most effective second-line regimen for the eradication of <em>H pylori</em> when first-line treatments fail.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Systematic reviews/meta-analysis, RCTs (blind or open-label).</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published papers (full text only).</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Adults (18 years and older) who have the following:</td>
</tr>
<tr>
<td>- Symptoms of dyspepsia</td>
<td>All subgroups (uninvestigated dyspepsia, ulcer dyspepsia, and functional dyspepsia) to be considered together.</td>
</tr>
<tr>
<td>- Positive test for <em>H pylori</em></td>
<td>It may be possible to perform subgroup analysis on gastric and peptic ulcer separately if data allows.</td>
</tr>
<tr>
<td>- Failed the first line eradication regimen recommended in Q5i</td>
<td>Subgroup analysis will be performed, if possible, on intolerance to penicillin.</td>
</tr>
<tr>
<td><strong>Include</strong></td>
<td></td>
</tr>
<tr>
<td>- Uninvestigated dyspepsia</td>
<td></td>
</tr>
<tr>
<td>- Ulcer dyspepsia (gastric or peptic)</td>
<td></td>
</tr>
<tr>
<td>- Functional/non ulcer dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Can consider together for analysis – same risk associated with failure</td>
<td></td>
</tr>
<tr>
<td><strong>Exclude</strong></td>
<td></td>
</tr>
<tr>
<td>- Studies with patients with <em>H pylori</em> infection being treated for diagnosis other than dyspepsia - gastric cancer, NSAID related GI irritation, or population screening.</td>
<td></td>
</tr>
<tr>
<td>- Studies where <em>H pylori</em> has not been confirmed (i.e. studies in high prevalence areas where infection is assumed)</td>
<td></td>
</tr>
<tr>
<td>- Endoscopically confirmed GORD</td>
<td></td>
</tr>
</tbody>
</table>
• Studies where 2nd line treatment was commenced within one month following completion of 1st line treatment.

**Intervention/indications**  
Comparison of the effectiveness of the following interventions – all compared to each other

**SEQUENTIAL THERAPY**

**TRIPLE THERAPY**
- Ab x 2 + PPI
- Ab x 1 + PPI + Bis
- Ab x 2 + H2RA
- Ab x 1 + H2RA + Bis

**QUADRUPLE THERAPY WITH BISMUTH**
- Ab x 3 + Bis
- Ab x 2 + PPI + Bis
- Ab x 2 + H2RA + Bis

**QUADRUPLE THERAPY WITH THREE ANTIBIOTICS**
- Ab x 3 + PPI
- Ab x 3 + H2RA

We will include ‘Individual/named antibiotics’ in two classes (Penicillins and Macrolides) but assume a class effect in all others

**Include**
- Studies comparing different lengths of the above listed regimens
- Follow up period to be a minimum of one month after treatment

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

**Control**
Include
- **SEQUENTIAL THERAPY**
- **MONOTHERAPY**
  - Ab alone
  - PPI alone
<table>
<thead>
<tr>
<th>Intervention Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2RA alone</td>
<td></td>
</tr>
<tr>
<td>DUAL THERAPY</td>
<td></td>
</tr>
<tr>
<td>Ab x 2</td>
<td></td>
</tr>
<tr>
<td>Ab x 1 + PPI</td>
<td></td>
</tr>
<tr>
<td>Ab x 1 + H2RA</td>
<td></td>
</tr>
<tr>
<td>TRIPLE THERAPY</td>
<td></td>
</tr>
<tr>
<td>Ab x 3</td>
<td></td>
</tr>
<tr>
<td>Ab x 2 + H2RA</td>
<td></td>
</tr>
<tr>
<td>Ab x 1 + H2RA + Bis</td>
<td></td>
</tr>
<tr>
<td>QUADRUPLE THERAPIES</td>
<td></td>
</tr>
<tr>
<td>Ab x 4</td>
<td></td>
</tr>
<tr>
<td>Ab x 3 + H2RA</td>
<td></td>
</tr>
<tr>
<td>Ab x 3 + Bis</td>
<td></td>
</tr>
<tr>
<td>Ab x 2 + H2RA + Bis</td>
<td></td>
</tr>
</tbody>
</table>

Sequential / Triple / Quad therapy with off-label antibiotic included
Each of the interventions will be compared to one another.
### Outcomes

<table>
<thead>
<tr>
<th>Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication rate</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on symptoms</td>
</tr>
<tr>
<td>Adherence to medication</td>
</tr>
<tr>
<td>Recurrence rate</td>
</tr>
<tr>
<td>Eradication by resistance status.</td>
</tr>
</tbody>
</table>

### Other criteria for inclusion/exclusion of studies

<table>
<thead>
<tr>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies with mixed populations (i.e. patients who have and have not tested positive for <em>H pylori</em>) will only be included if outcomes are clearly separated between these groups</td>
</tr>
<tr>
<td>Studies using off-label drugs in all arms for 2nd line</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line treatment (this will be covered in another question)</td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Non-pharmacological therapies (i.e. herbal, probiotics)</td>
</tr>
<tr>
<td>Studies assessing pharmacological therapies other than antibiotics, PPIs, H2RAs, chelates and complexes such as bismuth or sucralfate</td>
</tr>
<tr>
<td>Studies using unlicensed drugs in all arms of the trial</td>
</tr>
<tr>
<td>Studies comparing the effectiveness of cytoprotective or mucolytic agents</td>
</tr>
<tr>
<td>Any trial where patients are not randomized to 2nd line therapy</td>
</tr>
<tr>
<td>Studies where patients had received more than one previous attempt at eradication</td>
</tr>
<tr>
<td>Studies where drugs were given on sensitivity analysis.</td>
</tr>
</tbody>
</table>

We have assumed that:
- 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

- The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of
individual studies
- Data on all included studies will be extracted into evidence tables
- Where statistically possible, a meta-analytical approach will be used to give an overall summary effect (including the possibility of a network meta-analysis)
- All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarised in evidence statements
- Sub group analyses will be undertaken for the underlying cause of dyspepsia where appropriate.

Identified key background studies

**Systematic reviews**

**RCTs**

### Table 7: Review question 6

<table>
<thead>
<tr>
<th>Details</th>
<th>What is the effectiveness of laparoscopic fundoplication compared to medical management in patients with GORD?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To compare whether keyhole surgery or drug management is better for patients with heartburn and or reflux symptoms.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English only.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>RCTs, Quasi RCTs, systematic reviews.</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Published papers (full text only).</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>GORD/GERD/REFLUX</td>
</tr>
</tbody>
</table>
**Heartburn**  
- Acid exposure/indigestion  
- Waterbrash  
- Oesophagitis  
- With positive test for reflux (pH monitoring/manometry/doscopy)

**Include**
- Patients with symptoms >1year  
- Patients with stable symptoms for >3months (without change in medication)  
- Patients with symptoms expected to continue for 2 years

**Exclude**
- Patients <18 years  
- Previous Surgery for GORD, or oesophageal surgery  
- Patients with GORD and high grade dysplasia.

### Intervention/indications

**Include**
- Laparoscopic Fundoplication (either total/full, partial, or floppy)  
- Nissen  
- Anti reflux surgery

**Subgroup/sensitivity analysis**
- Total/full fundoplication vs other techniques (if data are available)

**Exclude**
- Open (Nissen) fundoplication  
- Endoscopic ablative procedures  
- Other minimally invasive surgical procedures.

### Control

**Include**
- Medical therapy with PPIs as at least one element of treatment  
- Esomепrozole  
- Lamпрozole  
- Omeprazole  
- Pantoprazole  
- Raberazole Sodium

**Exclude**
- Studies with H₂RAs (histamine receptor agonists) only (monotherapy)  
- Antacids  
- Other surgery.
## Dyspepsia and gastro-oesophageal reflux disease

Review protocols_searches_summary of modified GRADE

| Outcomes | - Health related QOL  
- Symptom control – dichotomous outcome  
- Acid reflux – 24 hr pH monitoring (% time <4)  
- Mortality  
- Medication use – frequency/dose  
- Serious adverse event – Bleeding, perforation, pneumothorax, dysphagia. |
| --- | --- |
| Other criteria for inclusion/exclusion of studies | **Include**  
- Robotic Laparoscopic – but treat same as ‘human’ laparoscopic  
(Interventional Procedures programme has concluded that these are in effect the same class of intervention)  

**Exclude**  
- Studies with follow up <1 year  
- Allocation by patient preference  
- Allocation by case selection  
- Studies of surgery vs sham surgery. |
| Search strategies | RCTs, Quasi RCTs, systematic reviews. |
| Review strategies | - The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies  
- Data on all included studies will be extracted into evidence tables  
- Where statistically possible, a meta-analytical approach will be used to give an overall summary effect  
- Dichotomous data will be pooled as relative risk and 95% CI if there is sufficient data  
- Adverse effects (incidence rates) will be pooled as relative risk and 95% CI  
- All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements  
- Sub group analysis for those with refractory / chronic GORD only vs mixed GORD population will be undertaken where appropriate. |
| Identified key background studies | **Systematic reviews**  


Markar SR(2010). Robotic vs laparoscopic Nissen fundoplication for gastro-
Dyspepsia and gastro-oesophageal reflux disease  
Review protocols_searches_summary of modified GRADE

<table>
<thead>
<tr>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wileman SM (2010). Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database of Systematic Reviews (3) 2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8: Review question 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Details</strong></td>
</tr>
<tr>
<td><strong>Review question</strong></td>
</tr>
<tr>
<td>What other management is effective for patients who do not respond to PPIs, H2 receptor antagonists, or H pylori eradication despite optimum primary care, or patients who have relapsed following surgery?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>To compare whether additional specialist medical management interventions are better than usual care for patients with refractory heartburn and or reflux symptoms.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td>English only.</td>
</tr>
</tbody>
</table>
### Study design

<table>
<thead>
<tr>
<th>Study design</th>
<th>RCTs, Quasi RCTs, systematic reviews, observational studies, cohort studies, case control studies.</th>
</tr>
</thead>
</table>

### Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Published papers (full text only).</th>
</tr>
</thead>
</table>

### Population

<table>
<thead>
<tr>
<th>Include</th>
<th>GORD / GERD / REFLUX</th>
</tr>
</thead>
</table>

- Heartburn
- Acid exposure
- Oesophagitis
- Dyspepsia
- Upper abdominal pain

**AND/PLUS**

- On 40mg dose PPI bd/ H2RA
- Patients with symptoms for >1 month
- Refractory
- Treatment failure
- Relapse
- Symptomatic
- Specialist
- Secondary care
- Consultant
- Hospital
- Secondary care

<table>
<thead>
<tr>
<th>Exclude</th>
<th>Patients &lt;18 years H2RA or PPI or H pylori eradication treatment naïve patients.</th>
</tr>
</thead>
</table>

### Intervention/indications

<table>
<thead>
<tr>
<th>Include</th>
<th>Split dose PPI</th>
</tr>
</thead>
</table>

- Nocturnal dose PPI
- Dual/combination therapy PPI plus H2RA treatment
- Prokinetics/dopamine receptor antagonists (metoclopramide, domperidone, itopride, mosapride)
- Laparoscopic (Nissen) fundoplication

<table>
<thead>
<tr>
<th>Exclude</th>
<th>Low dose antidepressants Tricyclics (and related)</th>
</tr>
</thead>
</table>

- Low dose antidepressants Monoamine-oxidase inhibitors
- Low dose antidepressants SSRIs
- Low dose antidepressants others, Venlafaxine Tryptophan, Reboxetine, Mirtazapine, fluoxetine, Duloxetine, Agomelatine
- Muscle relaxants (Baclofen, R-Baclofen, GABA Agonist, 5HT4 antagonist)
- Pain modifiers

---

Dyspepsia and gastro-oesophageal reflux disease

Review protocols_searches_summary of modified GRADE

National Institute for Health and Care Excellence 2014.

26
<table>
<thead>
<tr>
<th>Control</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Standard pharmacological interventions</td>
</tr>
<tr>
<td></td>
<td>- No intervention</td>
</tr>
<tr>
<td></td>
<td>- Self treatment.</td>
</tr>
</tbody>
</table>
### Outcomes

<table>
<thead>
<tr>
<th>Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health related QOL</td>
</tr>
<tr>
<td>Heartburn (% days free)</td>
</tr>
<tr>
<td>Remission of symptoms (dichotomous outcome)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid reflux – 24 hr pH monitoring (% time &lt;4)</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Adverse events (specific to each sub-question).</td>
</tr>
</tbody>
</table>

### Other criteria for inclusion/exclusion of studies

**Include**
- UK or Developed world setting
- Crossover trials

**Exclude**
- Studies with follow up <6 months
- Allocation by patient preference
- Allocation by case selection.

### Search strategies

RCTs, Quasi RCTs, systematic reviews, observational studies, cohort studies, case control studies.

### Review strategies

- The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies
- Data on all included studies will be extracted into evidence tables
- Where statistically possible, a meta-analytical approach will be used to give an overall summary effect using direct comparisons
- Dichotomous data will be pooled as relative risk and 95% CI if there is sufficient data
- Adverse effects (incidence rates) will be pooled as relative risk and 95% CI
- All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements
- Sub group analysis for those with refractory / chronic GORD only vs mixed GORD population will be undertaken where appropriate.

### Identified key background studies

**Systematic reviews**

Studies (these may be included within the systematic reviews listed above)

Khoury RM, Katz PO, Hammod R, Castell DO (1999). Bedtime ranitidine does
not eliminate the need for a second daily dose of omeprazole to suppress nocturnal gastric pH. Alimentary Pharmacology and Therapeutics 1999; 13(5):675-678


### Table 9: Review question 8

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td><strong>Status</strong></td>
</tr>
</tbody>
</table>
| **Population** | Include
| | • Barrett’s oesophagus
| | • Metaplasia/intestinal metaplasia
| | • Dyplasia
| | • Neoplasia
| | • Columnar AND epithelium/metaplasia
| | • Minimum length / distance from gastro-esophageal junction
| | • Histologically positive
| | • Precancer
| | • Goblet cells
| | • Mucosal inflammation
| | • Long/short AND segment
| | Minimum length of time since diagnosis with Barrett’s 6 months |
| | Exclude
| | • Patients <18 years
| | • Previous Surgery for GORD or oesophagastirc surgery.
| | • Previous surveillance programme
| | • Alarm signs for referral
| | • Other stratified patient cohort.
| | • Carcinoma |
- Studies that do not provide endoscopic criteria for definition of BO.

<table>
<thead>
<tr>
<th>Intervention/indications</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Quadrant/circumferential</td>
</tr>
<tr>
<td></td>
<td>Surveillance</td>
</tr>
<tr>
<td></td>
<td>Monitoring</td>
</tr>
<tr>
<td></td>
<td>Endoscopy AND gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>Repeat screening/mass screening</td>
</tr>
<tr>
<td></td>
<td>Protocol/programme</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endoscopy as needed</td>
</tr>
<tr>
<td></td>
<td>Spontaneous detection</td>
</tr>
<tr>
<td></td>
<td>Incidental identification</td>
</tr>
<tr>
<td></td>
<td>Ad hoc endoscopy</td>
</tr>
<tr>
<td></td>
<td>No surveillance.</td>
</tr>
</tbody>
</table>
### Outcomes
- Health related QOL – EQ 5D and SF-36 (EQ5D favoured, but I've found a few using SF-36)
- GORD/Health related QOL (using disease specific tools)
- Adverse event (Bleeding, oesophageal perforation, pneumothorax, anxiety)
- Mortality
- Endoscopic appearance
- Progression to adenocarcinoma and stage identified
- GP visits.

### Other criteria for inclusion/exclusion of studies
#### Include
- Superiority studies
- Non-inferiority studies
- Other treatment for Barrett’s standardized in both arms – drugs doses
- Standardised treatment protocol for patients that develop high grade dysplasia or cancer (resection oesophagectomy, or ablative endoscopic techniques)

#### Exclude
- Studies with follow up <3 years
- Studies with n<100.

### Search strategies
- RCTs, Quasi RCTs, systematic reviews, Non-randomised comparative studies, historically controlled studies (before and after), case control studies, cohort studies, case-series.

### Review strategies
- The NICE methodology checklist for RCTs will be used as a guide to appraise the quality of individual studies
- Data on all included studies will be extracted into evidence tables
- Where statistically possible, a meta-analytical approach will be used to give an overall summary effect
- Dichotomous data will be pooled as relative risk and 95% CI if there is sufficient data
- Adverse effects (incidence rates) will be pooled as relative risk and 95% CI
- All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements
- Sub group analysis for those with refractory/chronic GORD only vs mixed GORD population will be undertaken where appropriate.

### Identified key background studies
#### Systematic reviews
- NON RCT

#### Studies
- NON RCT
  - MacDonald CE (2000). Final results from 10 year cohort of patients undergoing
C.2 IS search strategies

C.2.1 Scoping searches

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

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

- 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

C.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)

C.2.2.1 Identification of evidence for clinical questions

30 The searches were conducted between November 2011 and May 2013. The aim of the searches was to identify evidence for each of the clinical questions being asked.
31 The MEDLINE search strategies are presented below. These were translated for use in all of the other databases.
32
33 Review question 1:
34 What is the diagnostic utility of non-urgent endoscopy in patients with signs and symptoms of dyspepsia or GORD?
35 Database: Ovid MEDLINE(R) <1946 to May Week 1 2013> (update search conducted on 11 December 2013)
36 Search Strategy:
37 1 exp Gastroesophageal Reflux/ (21027)
38 2 exp Duodenogastric Reflux/ (1565)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 gastroesophageal$) adj junction$).tw. (1923)
91  51  27 and 50 (331)
92  52  exp Diet/ (182864)
93  53  (diet$ or food$ or nutrition$).tw. (635091)
94  54  or/60-61 (271521)
95  55  27 and 54 (1151)
96  56  exp Smoking/ (115186)
97  57  (smok$ or cigarette$ or cigar$ or tobacco$).tw. (201167)
98  58  56 or 57 (228452)
99  59  27 and 58 (481)
100  60  exp Drinking Behavior/ (54011)
101  61  (alcohol$ or drink$).tw. (259963)
102  62  or/60-61 (271521)
103  63  27 and 62 (559)
104  64  body mass index/ (72094)
105  65  (body mass index$ or bmi$ or quetelet$ index$).tw. (110028)
Dyspepsia and gastro-oesophageal reflux disease

Review protocols_searches_summary of modified GRADE

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. (2090224)
125  84  or/79-83 (2174250)
126  85  33 and 84 (883)
127  86  exp Population Groups/ (197033)
128  87  eh.fs. (115162)
129  88  (ethnic$ or ethno$ or race$ or racial$).tw. (155305)
130  89  or/86-88 (342359)
131  90  27 and 89 (278)
132  91  animals/ not humans/ (3753959)
133  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)
134  93  92 not 91 (6294)
135  94  limit 93 to english language (5150)
136  95  incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos::tw. or predict::tw. or course::tw. (2070024)
137  96  (sensitiv: or diagnos:).mp. or di.fs. (3656151)

National Institute for Health and Care Excellence 2014.
Review Question 2:
Which risk factors indicate endoscopy in order to exclude Barrett’s oesophagus?

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

Search Strategy:
--------------------------------------------------------------------------------
1     Barrett Esophagus/ (5715)
2     barrett$.tw. (6721)
3     ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4244)
4     or/1-3 (10763)
5     exp Endoscopy/ (238917)
6     (endoscop$ or gastroscop$ or videoscop$).tw. (124065)
7     chromoendoscop$.tw. (519)
8     (esophagoscop$ or oesophagoscop$).tw. (1758)
9     or/5-8 (287817)
10    4 and 9 (3856)
11    risk factors/ (508949)
12    risk$.tw. (1087586)
13    or/11-12 (1274619)
14    10 and 13 (1162)
15    exp Hernia/ (58747)
16    (hernia$ or enterocele$).tw. (47909)
17    15 or 16 (71245)
18    10 and 17 (365)
19    Eructation/ (277)
20    (eructat$ or belch$ or burp$).tw. (971)
21    19 or 20 (1080)
22    10 and 21 (12)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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)
Review Question 3:

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

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

Search Strategy:

--------------------------------------------------------------------------------
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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. (35460)
267 31  General Surgery/ (31930)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 practice$)).tw. (87434)
292 55 Community Health Services/ (25377)
293 56 Community health nursing/ (17833)
294 57 ((walkin or walk-in or "walk in" or community health) adj3 (care or service$ or centre$ or center$ or clinic$ or facilit$)).tw. (4417)
295 58 or/45-57 (348834)
296 59 20 and 43 and 58 (483)
297 60 44 or 59 (2283)
298 61 animals/ not humans/ (3663211)
299 62 60 not 61 (2262)
Review Question 4:
What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease?

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

Search Strategy:

Review Question 5:
In patients with symptoms of dyspepsia who are positive for helicobacter pylori, which eradication regimens are the most clinically effective in the eradication of \textit{H pylori}?

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

Search Strategy:
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

Update search conducted on PubMed on 02 December 2013

Strategy:
National Institute for Health and Care Excellence 2014.

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 pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$).tw. (65001)
344 9 or/6-8 (66918)
345 10 exp Nitroimidazoles/ (14617)
346 11 (nitroimidazole$ or antiprotozoal$ or metronidazole$ or flagyl$ or tinidazole$ or 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 de-noltab$ or 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)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 fasigyn* or clarithromycin* or klaricid* or amox* or amix* or amoram* or amoxident* or alenamox* or rimoxallin* or bismuth* or tripotassium* or tri-potassium* or tri potassium* or de-noltab* or denoltag* or de noltab* or tetracyclin* or quinolon* or levofloxacin* or tavinic* or moxifloxacin* or avelox*[Title/Abstract])
384 Search (ppi* or proton pump* or omeprazole* or losec* or rabeprazole* or pari* or pantoprazole* or protium* or lansoprazole* or zoton* or esomeprazole* or 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])

Review Question 6:

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

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

Search Strategy:

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)
Review protocols_searches_summary of modified GRADE

Review Question 7:
What other medical management is effective for patients who do not respond to PPIs, H₂ receptor antagonists, or H pylori eradication despite optimum primary care, or patients who have relapsed following surgery?

Database: Ovid MEDLINE(R) <1946 to October Week 4 2012> (update search conducted on 12 December 2013)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

1  exp Gastroesophageal Reflux/ (20261)
2  exp Duodenogastric Reflux/ (1555)
3  (reflux$ or gord or gerd or ger).tw. (38634)
4  Esophageal Sphincter, Lower/ (536)
5  lower esophageal sphincter.tw. (3257)
6  lower oesophageal sphincter.tw. (907)
7  (les or los).tw. (16703)
8  Heartburn/ (1538)
9  heartburn$.tw. (3422)
10 pyros$.tw. (3254)
11 acid exposure.tw. (1885)
12 Dyspepsia/ (6883)
13 (dyspep$ or indigestion$).tw. (9823)
14 (regurg$ or waterbrash$).tw. (24575)
15 exp Esophagitis/ (9004)
16 (esophagi$ or oesophagi$).tw. (10881)
17 exp Gastritis/ (17381)
18 (gastro$ or gastr$ stas$).tw. (16348)
19 exp Abdominal Pain/ (23831)
20 ((abdom$ or stomach$) adj3 (ache$ or pain$ or discomfort$)).tw. (35707)
21 or/1-20 (172460)
22 Proton Pump Inhibitors/ (2569)
23 Omeprazole/ (8191)
24 (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$ or emozul$).tw. (65637)
25 or/22-24 (67572)
26 (nocturn$ or night$ or evening$ or bed$ or sleep$).tw. (246121)
27 ((split$ or separat$ or divid$ or even$ or spread$ or multipl$ or alter$ or chang$ or reduc$ or less$ or small$ or low$) adj3 dos$).tw. (196251)
28 25 and (26 or 27) (2830)
29 21 and 28 (753)
30 exp Histamine H2 Antagonists/ (18029)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

(1) h2ra$ or h2-ra$ or "h2 ra$".tw. (413)
(2) histamin$ adj3 (antagon$ or block$ or recep$).tw. (11117)
(3) h2$ adj3 (antagon$ or hist$ or block$ or recep$).tw. (14520)
(4) cimetidin$.tw. (10207)
(5) tagamet.tw. (95)
(6) ranitidin$.tw. (5384)
(7) zantac.tw. (56)
(8) famotidin$.tw. (1635)
(9) nizatidin$.tw. (354)
(10) axid.tw. (10)
(11) or/30-40 (35084)
(12) 25 and 41 (3913)
(13) 21 and 42 (1495)
(14) Dopamine Antagonists/ (9263)
(15) (dopamin$ adj3 (receptor$ or antagonist$)).tw. (27446)
(16) prokinetic$.tw. (1882)
(17) Metoclopramide/ (4448)
(18) (metoclopramide or maxolon).tw. (4925)
(19) Domperidone/ (1503)
(20) (domperidone or motilium).tw. (1835)
(21) (itopride or ganaton).tw. (64)
(22) (mosapride or biotonus).tw. (187)
(23) or/44-52 (38965)
(24) 21 and 53 (1474)
(25) exp Laparoscopy/ (62058)
(26) laparoscopes/ (3291)
(27) surgical procedures, Minimally Invasive/ (15264)
(28) (laparoscop$ or celioscop$ or keyhole$).tw. (72639)
(29) or/55-58 (95003)
(30) Fundoplication/ (3277)
(31) fundoplicat$.tw. (4067)
(32) gastroplicat$.tw. (48)
Review Question 8:
Should surveillance be used for patients with Barrett’s Oesophagus to detect progression to cancer, and improve survival?

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

Search Strategy:
--------------------------------------------------------------------------------
1  Barrett Esophagus/ (5504)
2  barrett$.tw. (6461)
3  ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4142)
4  ((metaplas$ or dysplasi$ or neoplas$) adj3 (column$ or intestin$ or epithel$ or oesophag$ or esophag$ or mucos$ or high-grade$ or low-grade$)).tw. (13822)
5  or/1-4 (21574)
6  exp Mass Screening/ (90868)
7  exp Population Surveillance/ (44090)
8  (screen$ or surveillan$ or monitor$).tw. (843147)
9  or/6-8 (896405)
10 exp Endoscopy/ (231412)
11 endoscop$.tw. (116970)
12 chromoendoscop$.tw. (489)
13 (esophagoscop$ or oesophagoscop$).tw. (1731)
14 exp Biopsy/ (205812)
15 biops$.tw. (251781)
16 or/10-15 (604770)
Broad update search for all review questions (apart from RQ5) conducted on PubMed on 11 December 2013

Strategy:

Search (#21 or #23)
Search (#19 and #20)
Search (#19 and #22)
Search ("2013/12/09"[Date-Entrez] : "3000"[Date-Entrez])
Search publisher[sb]
Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
Search (((metaplas* or dysplasi* or neoplasi*[Title/Abstract])) AND (epithel* or oesophag* or esophag* or mucos*[Title/Abstract]))
Search (((column* or speciali* or intestinali*[Title/Abstract])) AND (epithel* or oesophag* or esophag* or mucos*[Title/Abstract]))
Search (((((reflux*[Title/Abstract]) NOT (coronar* or heart* or mitral* or vascular* or pulmonar* or vesico* or uter* or laryn*[Title/Abstract])))])
Search lower esophageal sphincter[Title/Abstract]
Search lower oesophageal sphincter[Title/Abstract]
Search pyros*[Title/Abstract]
Search acid exposure[Title/Abstract]
Search esophagit*[Title/Abstract]
Search oesophagit*[Title/Abstract]
Search gord[Title/Abstract]
Search gerd[Title/Abstract]
Search ger[Title/Abstract]
Search indigestion*[Title/Abstract]
Search barrett*[Title/Abstract]
Search heartburn[Title/Abstract]
Search (((acid*[Title/Abstract]) AND regurg*[Title/Abstract])))
Search dyspep*[Title/Abstract]
Search waterbrash*[Title/Abstract]
Study design filters

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

Specific systematic reviews filter

Appended to review questions 4 and 7

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

Broad systematic reviews filter

Appended to review questions 5 and 6

1. Meta-Analysis.pt. (37837)
2. Meta-Analysis as Topic/ (12594)
3. Review.pt. (1757173)
4. exp Review Literature as Topic/ (6618)
5. (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (45065)
6. (review$ or overview$).ti. (240634)
7. (systematic$ adj4 (review$ or overview$)).tw. (40425)
8. ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3110)
9. ((studies or trial$) adj1 (review$ or overview$)).tw. (6557)
10. (integrat$ adj2 (research or review$ or literature)).tw. (3111)
11. (pool$ adj1 (analy$ or data)).tw. (7682)
12. (handsearch$ or (hand adj2 search$)).tw. (4484)
13. (manual$ adj2 search$).tw. (2443)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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)

6.2.3 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 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)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

661 15  exp Duodenogastic 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$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (82446)
670 24  ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (1286)
671 25  or/22-24 (264951)
672 26  21 or 25 (428356)

Health economics studies for Barrett’s oesophagus

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

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

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

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

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

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

Search Strategy:
--------------------------------------------------------------------------------
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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)

National Institute for Health and Care Excellence 2014.
54
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$).tw. (998)
735  40  38 or 39 (1111)
736  41  27 and 40 (126)
737  42  Polymorphism, Single Nucleotide/ (57063)
738  43  single nucleotide polymorphism.tw. (12199)
739  44  or/42-43 (59882)
740  45  27 and 44 (11)
741  46  ((paediatric or pediatric) adj reflux$).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-esophageal$) adj junction$).tw. (1937)
746  51  27 and 50 (332)
747  52  exp Diet/ (183353)
748  53  (diet$ or food$ or nutrition$).tw. (636973)
749  54  52 or 53 (700671)
750  55  27 and 54 (1154)
751  56  exp Smoking/ (115460)
752  57  (smok$ or cigarette$ or cigar$ or tobacco$).tw. (201772)
753  58  56 or 57 (229102)
754  59  27 and 58 (484)
755  60  exp Drinking Behavior/ (54157)
756  61  (alcohol$ or drink$).tw. (260642)
757  62  or/60-61 (272215)
758  63  27 and 62 (559)
Health economics questions on Q2: Symptoms indicating endoscopy for Barrett’s oesophagus plus economic evaluations filter

The searches were undertaken in January 2013. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence.
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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

Search Strategy:

--------------------------------------------------------------------------------
1  Barrett Esophagus/ (5721)
2  barrett$.tw. (6728)
3  ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4248)
4  or/1-3 (10773)
5  exp Endoscopy/ (239333)
6  (endoscop$ or gastroscop$ or videoscop$).tw. (124226)
7  chromoendoscop$.tw. (520)
8  (esophagoscop$ or oesophagoscop$).tw. (1759)
9  or/5-8 (288290)
10  4 and 9 (10773)
11  risk factors/ (509982)
12  risk$.tw. (1089808)
13  or/11-12 (1277173)
14  10 and 13 (1162)
15  exp Hernia/ (58796)
16  (hernia$ or enterocele$).tw. (47965)
17  15 or 16 (71313)
18  10 and 17 (365)
19  Eructation/ (277)
20  (eructat$ or belch$ or burp$).tw. (971)
21  19 or 20 (1080)
22  10 and 21 (12)
23  Chest Pain/ (8528)
24  ((chest or thora$) adj3 (pain$ or ache$ or discomfort$)).tw. (23962)
25  Heartburn/ (1546)
26  (heartburn$ or pyros$).tw. (6758)
27  or/23-26 (33479)
28  10 and 27 (308)

National Institute for Health and Care Excellence 2014. 57
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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

National Institute for Health and Care Excellence 2014.
Economic searches on Review Question 3: Dyspepsia – referral to consultancy led services

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

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

Search Strategy:

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

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

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

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

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

Search Strategy:

1 exp Gastroesophageal Reflux/ (21027)
2 exp Duodenogastric Reflux/ (1565)
3 (reflux$ or gord or gerd or ger).tw. (39779)
4 exp Esophagitis/ (9302)
5 (esophagi$ or oesophagi$).tw. (11290)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

62

Health economics studies on RQ 5 \textit{H pylori}

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

1. sequen$.tw. (780022)
2. tripl$.tw. (57062)
3. quadrupl$.tw. (6508)
4. ((standard$ or convention$) adj3 (therap$ or treat$ or regim$)).tw. (72267)
5. or/1-4 (902378)
6. Proton Pump Inhibitors/ (2108)
7. Omeprazole/ (8195)
8. (ppi$ or proton pump$ or omeprazole$ or losec$ or rabeprazole$ or pariet$ or pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexium$).tw. (63366)
9. or/6-8 (65253)
10. exp Nitroimidazoles/ (14387)
11. (nitroimidazole$ or antiprotozoal$ or metronidazole$ or flagyl$ or tinidazole$ or fasigyn$).tw. (12981)
12. Clarithromycin/ (4696)
13. (clarithromycin$ or klaricid$).tw. (5782)
14. exp Amoxicillin/ (8484)
15. (amox$ or amix$ or amoram$ or amoxident$ or alenamox$ or rimoxallin$).tw. (11714)
16. Bismuth/ (4343)
17. (bismuth$ or tripotassium$ or tri-potassium$ or tri potassium$ or de-noltab$ or denoltab$ or de noltab$).tw. (4148)
18. exp Tetracyclines/ (38179)
19. tetracyclin$.tw. (25264)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

991 20  exp Quinolones/ (31777)
992 21  (quinolon$ or levofoxacin$ 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 fundoplication compared to medical management in patients with GORD
1003 The searches were undertaken in November 2011. Search filters to retrieve economic evaluations and quality of life papers were appended to the following search strategy to identify relevant evidence
1004 Database: Ovid MEDLINE(R) <1948 to November Week 3 2011>
1005--------------------------------------------------------------------------------
1006 1     exp Gastroesophageal Reflux/ (19796)
1007 2     exp Duodenogastric Reflux/ (1567)
1008 3     (reflux$ or gord or gerd or ger).tw. (37759)
1009 4     Esophageal Sphincter, Lower/ (466)
1010 5     lower esophageal sphincter.tw. (3192)
1011 6     lower oesophageal sphincter.tw. (893)
1012 7     (les or los).tw. (15977)
1013 8     Heartburn/ (1461)
1014 9     heartburn$.tw. (3294)
1015 10  pyros$.tw. (2439)
1016 11  acid exposure.tw. (1801)
1017 12  Dyspepsia/ (6800)
1018 13  (dyspep$ or indigestion$).tw. (9598)
1019 14  (regurg$ or waterbrash$).tw. (23945)
1020 15  exp Esophagitis/ (8866)

National Institute for Health and Care Excellence 2014.
63
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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

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

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

Search Strategy:

1 exp Gastroesophageal Reflux/ (21834)
2 exp Duodenogastric Reflux/ (1598)
3 (reflux$ or gord or gerd or ger).tw. (41116)
4 Esophageal Sphincter, Lower/ (636)
5 lower esophageal sphincter.tw. (3396)
6 lower oesophageal sphincter.tw. (951)
7 (les or los).tw. (18554)
8 Heartburn/ (1711)
9 heartburn$.tw. (3837)
10 pyros$.tw. (4848)
11 acid exposure.tw. (2136)
12 Dyspepsia/ (7239)
13 (dyspep$ or indigestion$).tw. (10520)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 pantoprazole$ or protium$ or lansoprazole$ or zoton$ or esomeprazole$ or nexion$ or emozul$).tw. (73807)
1068 25 or/22-24 (75976)
1069 26 (nocturn$ or night$ or evening$ or bed$ or sleep$).tw. (265507)
1070 27 ((split$ or separat$ or divi$ or even$ or spread$ or multipl$ or alter$ or chang$ or reduc$ or less$ or small$ or low$) adj3 dos$).tw. (212809)
1071 28 25 and (26 or 27) (3312)
1072 29 21 and 28 (952)
1073 30 exp Histamine H2 Antagonists/ (18438)
1074 31 (h2ra$ or h2-ra$ or "h2 ra$").tw. (456)
1075 32 (histamin$ adj3 (antagon$ or block$ or recep$)).tw. (11644)
1076 33 (h2$ adj3 (antagon$ or hist$ or block$ or recep$)).tw. (15499)
1077 34 cimetidin$.tw. (10324)
1078 35 tagamet.tw. (97)
1079 36 ranitidin$.tw. (5605)
1080 37 zantac.tw. (58)
1081 38 famotidin$.tw. (1728)
1082 39 nizatidin$.tw. (375)
1083 40 axid.tw. (11)
1084 41 or/30-40 (36871)
1085 42 25 and 41 (4294)
1086 43 21 and 42 (1658)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 biotonus).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>
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

Search Strategy:

1. Barrett Esophagus/ (5540)
2. barrett$.tw. (6502)
3. ((column$ or speciali$ or intestinali$) adj3 (epithel$ or oesophag$ or esophag$ or mucos$)).tw. (4150)
4. ((metaplas$ or dysplasi$ or neoplasi$) adj3 (column$ or intestin$ or epithel$ or oesophag$ or esophag$ or mucos$ or high-grade$ or low-grade$)).tw. (13889)
5. or/1-4 (21677)
6. exp Mass Screening/ (91380)
7. exp Population Surveillance/ (44528)
8. (screen$ or surveillan$ or monitor$).tw. (850390)
9. or/6-8 (903995)
10. exp Endoscopy/ (232503)
11. endoscop$.tw. (117555)
12. chromoendoscop$.tw. (493)
13. (esophagoscop$ or oesophagoscop$).tw. (1734)
14. exp Biopsy/ (206772)
15. biops$.tw. (253125)
16. or/10-15 (607756)
17. 9 and 16 (43821)
18. 5 and 17 (2236)

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

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

1. Dyspepsia/ (7350)
2. (dyspep$ or indigestion$).tw. (10747)
3. (regurg$ or waterbrash$).tw. (26570)
4. Heartburn/ (1741)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (95901)
1174 24  ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (1544)
1175 25  or/22-24 (305698)
1176 26  21 or 25 (487765)
1177 27  "Value of Life"/ (5495)
1178 28  Quality-Adjusted Life Years/ (7347)
1179 29  quality adjusted life.tw. (6165)
1180 30  (qaly$ or qald$ or qale$ or qtime$).tw. (5151)
1181 31  disability adjusted life.tw. (1204)
1182 32  daly$.tw. (1179)
1183 33  Health Status Indicators/ (21035)
1184 34  (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15680)
Search Strategy:

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

---

Uncommented search strategy:

35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1085)
36 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2653)
37 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20)
38 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (334)
39 (euroqol or euro qol or eq5d or eq 5d).tw. (3796)
40 (hye or hyes).tw. (53)
41 health$ year$ equivalent$.tw. (37)
42 (health adj3 state adj3 utilit$).tw. (335)
43 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (5348)
44 (hui or hui1 or hui2 or hui3).tw. (884)
45 disutili$.tw. (214)
46 rosser.tw. (73)
47 quality of wellbeing.tw. (6)
48 quality of well-being.tw. (353)
49 qwb.tw. (173)
50 willingness to pay.tw. (2162)
51 standard gamble$.tw. (673)
52 time trade off.tw. (741)
53 time tradeoff.tw. (212)
54 tto.tw. (585)
55 (preferen$ weight$ or health state preferen$).tw. (257)
56 or/27-55 (62401)
57 26 and 56 (1701)
58 limit 57 to english language (1615)
59 limit 58 to ed=20120201-20131204 (277)

---

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 03, 2013>
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 intestine$ or gastric$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (5670)
1245  24  ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (103)
1246  25  or/22-24 (5726)
1247  26  21 or 25 (14913)
1248  27  "Value of Life"/ (0)
1249  28  Quality-Adjusted Life Years/ (0)
1250  29  quality adjusted life.tw. (574)
1251  30  (qaly$ or qald$ or qale$ or qtime$).tw. (469)
1252  31  disability adjusted life.tw. (153)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

1255 32 daly$.tw. (140)
1256 33 Health Status Indicators/ (0)
1257 34 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirty six or sf thirty six or shortform thirty six or short form thirty six or short form thirty six).tw. (1204)
1258 35 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sf six or shortform six or short form six).tw. (373)
1259 36 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (305)
1260 37 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sf sixteen or shortform sixteen or short form sixteen).tw. (3)
1261 38 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (11)
1262 39 (euroqol or euro qol or eq5d or eq 5d).tw. (449)
1263 40 (hye or hyes).tw. (2)
1264 41 health$ year$ equivalent$.tw. (2)
1265 42 (health adj3 state adj3 utilit$).tw. (41)
1266 43 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (450)
1267 44 (hui or hui1 or hui2 or hui3).tw. (82)
1268 45 disutili$.tw. (22)
1269 46 rosser.tw. (1)
1270 47 quality of wellbeing.tw. (2)
1271 48 quality of well-being.tw. (9)
1272 49 qwb.tw. (5)
1273 50 willingness to pay.tw. (234)
1274 51 standard gamble$.tw. (31)
1275 52 time trade off.tw. (57)
1276 53 time tradeoff.tw. (7)
1277 54 tto.tw. (55)
1278 55 (preferen$ weight$ or health state preferen$).tw. (23)
1279 56 or/27-55 (3571)
1280 57 26 and 56 (64)
1281 58 limit 57 to english language (60)
1282 59 Database: Embase <1980 to 2013 Week 48>

National Institute for Health and Care Excellence 2014.
Search Strategy:

1. dyspepsia/ (24578)
2. (dyspep$ or indigestion$).tw. (15222)
3. indigestion/ (1623)
4. (regurg$ or waterbrash$).tw. (37061)
5. heartburn/ (9009)
6. heartburn$.tw. (5633)
7. pyros$.tw. (7133)
8. acid exposure.tw. (2969)
9. exp peptic ulcer/ (99843)
10. ((peptic$ or gastr$ or duoden$ or stomach$) adj3 ulcer$).tw. (63195)
11. exp esophagit$ (23422)
12. (esophagi$ or oesophagi$).tw. (17107)
13. exp gastritis/ (50481)
14. (gastrit$ or gastr$ stas$).tw. (22739)
15. exp gastroesophageal reflux$ (43044)
16. exp duodenogastric reflux$ (2508)
17. laryngopharyngeal reflux$ (814)
18. (reflux$ or gord or gerd or ger).tw. (59125)
19. lower esophagus sphincter/ (9546)
20. lower esophageal sphincter.tw. (4406)
21. lower oesophageal sphincter.tw. (1121)
22. (les or los).tw. (40231)
23. or/1-22 (333773)
24. gastrointestinal tumor/ (9980)
25. exp stomach cancer/ (63618)
26. exp esophagus cancer/ (37040)
27. exp intestine cancer/ (158216)
28. ((stomach$ or oesoph$ or esoph$ or intestin$ or gastric$) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (124439)
29. ((upper digestive$ or upper gastr$ or upper gi) adj3 (cancer$ or carcinoma$ or adenocarcinoma$ or neoplasm$ or tumor$ or tumour$ or malign$)).tw. (2091)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 thirty six or shortform thirty six or short form thirty six or short form thirty six).tw. (22104)
1332  40 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sf six or shortform six or short form six).tw. (1435)
1333  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)
1334  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)
1335  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)
1336  44 (euroqol or euro qol or eq5d or eq 5d).tw. (6317)
1337  45 (hye or hyes).tw. (84)
1338  46 health$ year$ equivalent$.tw. (43)
1339  47 (health adj3 state adj3 utilit$).tw. (542)
1340  48 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (7535)
1341  49 (hui or hui1 or hui2 or hui3).tw. (1206)
1342  50 disutili$.tw. (351)
1343  51 rosser.tw. (88)
1344  52 quality of wellbeing.tw. (19)
1345  53 quality of well-being.tw. (372)
1346  54 qwb.tw. (192)
1347  55 willingness to pay.tw. (3188)
1348  56 standard gamble$.tw. (770)
1349  57 time trade off.tw. (978)
1350  58 time tradeoff.tw. (224)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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  Search Hits
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  gastritt* 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
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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

Search ("2013/12/02"[Date - Publication] : "3000"[Date - Publication])  13997
#5     Search (#1 or #4)  427055
#4     Search (#2 and #3)  67921

Search (dyspep* or indigestion or regurg* or waterbrash or heartburn or pyros* or â€œacid exposureâ€• or
 esophagi* or oesophagi* or gastrit* or gastr* or stas* or reflux* or gord or gerd or ger or â€œlower esophageal
 sphincterâ€• or les or los[Title/Abstract])  402629
#3     Search ulcer*[Title/Abstract]  157670

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   National Institute for Health and Care Excellence 2014.
Notes:
PubMed – only limited by date, adding the publisher limit retrieved too many results (not necessarily recent).

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

Specific economic evaluations filter
1. "Value of Life"/ (5218)
2. Quality-Adjusted Life Years/ (5682)
3. quality adjusted life.tw. (4551)
4. (qaly$ or qald$ or qale$ or qtime$).tw. (3807)
5. disability adjusted life.tw. (870)
6. daly$.tw. (882)
7. Health Status Indicators/ (17920)
8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirty six or sf thirty six or shortform thirty six or short form thirty six or short form thirty six).tw. (12459)
9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (898)
10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (1936)
11. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (18)
12. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (308)
13. (euroqol or euro qol or eq5d or eq 5d).tw. (2690)
14. (hye or hyes).tw. (52)
15. health$ year$ equivalent$.tw. (36)
16. (health adj3 state adj3 utilit$).tw. (232)
17. (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw. (4170)
18. (hui or hui1 or hui2 or hui3).tw. (698)
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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.
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

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 thirtysix or short form thirty six).tw.
1493 9  (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
1494 10  (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
1495 11  (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
1496 12  (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
1497 13  (euroqol or euro qol or eq5d or eq 5d).tw.
1498 14  (hye or hyes).tw.
1499 15  health$ year$ equivalent$.tw.
1500 16  (health adj3 state adj3 utilit$).tw.
1501 17  (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw.
1502 18  (hui or hui1 or hui2 or hui3).tw.
1503 19  disutili$.tw.
1504 20  rosser.tw.
1505 21  quality of wellbeing.tw.

National Institute for Health and Care Excellence 2014.
C.3 Summary of the modified GRADE approach

For the review questions [2014 update]:

- **Review question 1:** When should (and with what indications) patients with uninvestigated dyspepsia be referred for endoscopy for further investigation and review of treatment plan?
- **Review question 2:** Which risk factors indicate endoscopy in order to exclude Barrett’s oesophagus?
- **Review question 3:** Which patient characteristics/clinical indicators/criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed GORD managed in primary care to a consultant led medical or surgical service (specialist services)?

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

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

**Quality appraisal using modified-GRADE approach**

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

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

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

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

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

In prognostic study (or clinical prediction model), these varying degrees of risk of bias in a study do not apply same as in an intervention study. This is because in a multivariate regression model (MRM), the sources of the risk of bias commonly came from how the data of the individual risk factors or predictors was collected as a whole in a study, and what kinds of adjustment were made in the MRM regarding baseline confounders and covariates.

Hence, the risk of bias in a study would have impacted the MRM as whole (i.e. all risk factors or predictors entered in the MRM equally). Therefore, the quality of an individual study would apply across to all risk factors or predictors in that particular individual study.

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

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

Section 2: Criteria and downgrading

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

<table>
<thead>
<tr>
<th>GRADE criteria</th>
<th>Hayden (2006) QUIPS criteria, plus other statistical rules</th>
<th>Downgrading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
<td>1) Prospective study.</td>
<td>Downgrade 1 level if either (1) or (2) or both were not satisfied</td>
</tr>
<tr>
<td></td>
<td>2) Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.*</td>
<td>If there are more than one included studies,</td>
</tr>
</tbody>
</table>

Note*: To adjust potential confounders that are not
Dyspepsia and gastro-oesophageal reflux disease
Review protocols_searches_summary of modified GRADE

<table>
<thead>
<tr>
<th>Part of the independent variables (risk factors) being studied.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downgrade 1 level if either (1) or (2) or both were not satisfied in &gt;50% of the included studies.</td>
</tr>
</tbody>
</table>

**Indirectness**

1) The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results.
2) The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias.
3) The outcome of interest is adequately measured in study participants, sufficient to limit potential bias.

i) Downgrade 1 level if either (1) or (2) or (3) were not satisfied.
ii) Downgrade 2 levels if more than 2 criteria were not satisfied.

If there are more than one included studies, downgrade 1 level if >50% of the included studies been downgraded due to i).
If there are more than one included studies, downgrade 2 levels if >50% of the included studies been downgraded due to ii).

**Inconsistency**

1) Same direction of effect estimates across all different studies.
2) Overlaps of 95%CI.

Downgrade 1 level if either (1) or (2) or both were not satisfied.

Note: this criterion is not applicable to single study.

**Imprecision**

The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results (i.e. multivariate analysis - logistic regression model):
1) Model diagnostics: Assumption of normality (1a); Multicollinearity (1b); Goodness-of-fit (1c).
2) Reproducibility (validation).

i) Downgrade 1 level if either (1) or (2) was not satisfied.
ii) Downgrade 2 levels if both (1) and (2) were not satisfied.

If there are more than one included studies, downgrade 2 levels if >50% of the included studies been downgraded due to i) or ii).

**Other considerations**

1) Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias.

Downgrade 1 level if (1) was not satisfied.

If there are more than one included studies, downgrade 1 level if >50% of the included studies been downgraded.
For the quality appraisal for individual studies for review question 2, please see below. For the full modified-GRADE profiles, please also see appendix F.

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

Table below shows review question 2: Quality appraisal of individual studies – Modified GRADE – Criteria adapted from the Hayden et al (2006) checklist.
<table>
<thead>
<tr>
<th>Risk of bias (Study design limitations)</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams (2008)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Ford (2005)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Johanson (2007)</td>
<td>Yes, No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Voutilainen (2006)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Jemal (2011)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Omer (2012)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Lam (2008)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Maroni (2011)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Thrift (2012)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>All Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Khot (2012)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Nielsen (2012)</td>
<td>Yes, No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Rubenstram (2010)</td>
<td>Yes, No</td>
<td>No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Bo (2006)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Conio (2002)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Fan (2009)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Thrift (2013)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Campos (2001)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Ebbldt (2001)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Garson (2001)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Garson (2007)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Koek (2008)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Lieberman (1997)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Wang (2008)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>De Mag (1999)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Noordt (1997)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Dietz (2006)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Estebay (2008)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Romero (2002)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Thompson (2009)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Jacobson (2011)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Stein (2005)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Dickman (2005)</td>
<td>Yes, No</td>
<td>Yes, No</td>
<td>Yes</td>
<td>All Yes</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Prospective*: 1

**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 part of the independent variables (risk factors) being studied.

**The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results.**

**The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias.**

**The outcome of interest is adequately measured in study participants, sufficient to limit potential bias.**

**Some direction of effect estimates across different studies.**

**The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results (i.e. multivariate analysis - logistic regression model).**

**Model diagnostics: Assumption of normality (1a); Multicollinearity (1b); Goodness-of-fit (1c).**

**Reproducibility (variance) (2)***

**Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias.**

**Risk bias:** (1): YES, (2): unable to adjust GORD symptoms, etc.