

# 1 Appendix C: Review Protocols & Search Strategy

## A.1.1 Scoping searches

Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in October 2012 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

Guidelines/website	Systematic review/economic evaluations
<ul style="list-style-type: none"> <li>• Audit Commission</li> <li>• British Dietetic Association</li> <li>• British Nutrition Foundation</li> <li>• British Society of Gastroenterology</li> <li>• British Society of Paediatric Gastroenterology, Hepatology and Nutrition</li> <li>• Care Quality Commission</li> <li>• Coeliac UK</li> <li>• COMET</li> <li>• Department of Health</li> <li>• Guidelines International Network (GIN)</li> <li>• Healthcare Improvement Scotland</li> <li>• Health Protection Agency</li> <li>• King's Fund</li> <li>• National Audit Office</li> <li>• National Patient Safety Agency</li> <li>• National Institute for Health and Clinical Excellence (NICE) - published &amp; in development guidelines</li> <li>• National Institute for Health and Clinical Excellence (NICE) - Topic Selection</li> <li>• National Institute for Innovation and Improvement</li> <li>• National Patient Safety Agency</li> <li>• National Prescribing Centre</li> <li>• NHS Business Services Authority</li> <li>• NHS Evidence</li> <li>• NHS Information Centre</li> <li>• NHS Scotland</li> <li>• NHS Wales</li> <li>• New Zealand Guidelines Group</li> <li>• Primary Care Society for Gastroenterology</li> <li>• Prodigy (formerly Clinical Knowledge Summaries)</li> <li>• Royal Colleges</li> <li>• Royal Pharmaceutical Society of Great Britain</li> <li>• Royal Society of Medicine</li> <li>•</li> </ul>	<ul style="list-style-type: none"> <li>• BMJ Clinical Evidence</li> <li>• Cochrane Database of Systematic Reviews (CDSR)</li> <li>• Database of Abstracts of Reviews of Effects (DARE)</li> <li>• DUETS</li> <li>• Health Economic Evaluations Database (HEED)</li> <li>• Health Technology Assessment (HTA) Database</li> <li>• NHS Economic Evaluation Database (NHS EED)</li> <li>• NIHR Health Technology Assessment</li> <li>• NIHR Health Services and Delivery Research (HS&amp;DR) Programme</li> <li>• PROSPERO</li> <li>• TRIP Database</li> </ul>

- Scottish Intercollegiate Guidelines Network (SIGN)
- Scottish Medicines Consortium
- Social Care Institute for Excellence (SCIE)
- UK National Screening Committee
- US National Guideline Clearinghouse

### **A.1.2 Main searches**

Sources searched for the guideline

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

### **A.1.3 Identification of evidence for clinical questions**

The searches were conducted between May 2013 and July 2014. The re-run searches took place in December 2014. The aim of the searches was to identify evidence for each of the clinical questions being asked.

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

## **A.2 Review question search strategies**

### **A.2.1 Search strategy review questions 4.1, 4.2, & 4.3**

Which presenting features raise suspicion of coeliac disease?

- 4.1 What are the clinical signs and symptoms which raise suspicion of coeliac disease?
- 4.2 What populations have an increased risk of developing coeliac disease?
  - i. Co-existing diseases
  - ii. Other factors (ie. first-degree relatives)
- 4.3 What are the long-term consequences of undiagnosed or untreated coeliac disease?

**Table 1: search strategy 4.1, 4.2, & 4.3**

Medline Strategy, searched 24th July 2013 – 28th August 2014	
Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>	
Search Strategy:	
1	(coeliac adj4 disease).tw.
2	(celiac adj4 disease).tw.
3	(coeliac adj4 sprue).tw.
4	(celiac adj4 sprue).tw.
5	((nontropical or non tropical) adj4 sprue).tw.
6	((celiac or coeliac) adj4 syndrome).tw.
7	(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8	((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9	Celiac Disease/
10	or/1-9
11	(occurrence or prevalen* or incidence or epidemiolog*).tw.
12	(seroprevalence or seroepidemiol*).tw.
13	Prevalence/
14	Incidence/
15	Epidemiology/
16	or/11-15
17	10 and 16
18	(first adj4 relative*).tw.
19	famil*.tw.
20	Family/
21	Mothers/
22	Fathers/
23	Parents/
24	Nuclear Family/
25	Siblings/
26	Child/
27	Spouses/
28	(mother* or father* or brother* or sister* or parent* or child* or son* or daughter* or husband* or wife* or spouse* or aunt* or uncle* or sibling* or offspring or cousin*).tw.
29	genetic*.tw.
30	Genetic Predisposition to Disease/
31	Risk Factors/
32	risk*.tw.
33	or/18-28
34	or/29-32
35	10 and 33 and 34
36	17 or 35
37	undiagnosed.tw.
38	silent.tw.
39	untreated.tw.
40	((delay* or error*) adj4 diagnos*).tw.
41	(Unrecognised or unrecognized).tw.
42	Hidden.tw.
43	Missed.tw.
44	Misdiagnos*.tw.
45	Undetect*.tw.
46	Delayed Diagnosis/

**Medline Strategy, searched 24th July 2013 – 28th August 2014****Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>****Search Strategy:**

47 exp Diagnostic Error/  
 48 or/37-47  
 49 10 and 48  
 50 (severe adj4 sepsis).tw.  
 51 septicemia\*.tw.  
 52 (blood adj4 poisoning).tw.  
 53 Sepsis/  
 54 Rickets.tw.  
 55 Rickets/  
 56 ((nonhodgkin\* or non-hodgkin\*) adj4 lymphoma\*).tw.  
 57 Lymphoma, Non-Hodgkin/  
 58 or/51-57  
 59 10 and 58  
 60 49 or 59  
 61 exp Diabetes Mellitus, Type 1/  
 62 (diabet\* or (wolfram adj4 syndrome) or (impaired adj4 glucose adj4 intolerance)).tw.  
 63 exp Thyroiditis/  
 64 thyroiditides.tw.  
 65 (thyroiditis or (hashimoto adj4 disease)).tw.  
 66 Addison Disease/  
 67 (addison\* adj4 disease).tw.  
 68 ((adrenal or adrenocortical) adj4 insufficiency).tw.  
 69 hypocortisolism.tw.  
 70 hypocorticism.tw.  
 71 hypoadrenalism\*.tw.  
 72 exp Lupus Erythematosus, Systemic/  
 73 lupus.tw.  
 74 Hepatitis, Autoimmune/  
 75 (auto adj4 immune adj4 (liver or hepatitis)).tw.  
 76 Turner Syndrome/  
 77 (turner\* adj4 syndrome\*).tw.  
 78 (bonnevie-ullrich adj4 syndrome\*).tw.  
 79 (gonadal adj4 dysgenesis).tw.  
 80 exp Alopecia/  
 81 (alopecia or (follicular adj4 mucinosis)).tw.  
 82 baldness.tw.  
 83 IgA Deficiency/  
 84 iga deficienc\*.tw.  
 85 Down Syndrome/  
 86 (down\* adj4 syndrome\*).tw.  
 87 (trisomy adj4 (hypocorticism or "21")).tw.  
 88 Williams Syndrome/  
 89 (william\* adj4 syndrome\*).tw.  
 90 (elfin adj4 face\* adj4 syndrome\*).tw.  
 91 Sjogren's Syndrome/  
 92 ((Sjogren\* or sjoegren\* or sicca\*) adj4 Syndrome\*).tw.  
 93 Comorbidity/  
 94 (co-morbid\* or comorbid\* or co-exist\* or coexist\* or co-occur\* or cooccur\*).tw.  
 95 or/61-94

**Medline Strategy, searched 24th July 2013 – 28th August 2014****Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>****Search Strategy:**

- 96 10 and 95
- 97 exp Abdominal Pain/
- 98 (abdominal adj4 (distension or pain or bloat\* or cramp\*)).tw.
- 99 (stomach adj4 (distension or pain or bloat\* or cramp\*)).tw.
- 100 exp Diarrhea/
- 101 (diarrhoea or diarrhea).tw.
- 102 Constipation/
- 103 constipat\*.tw.
- 104 (colonic adj4 inertia).tw.
- 105 (irritable adj4 colon).tw.
- 106 ((mucous or mucus) adj4 (colitis or colotides)).tw.
- 107 Steatorrhea/
- 108 (steatorrhoea or steatorrhea).tw.
- 109 Flatulence/
- 110 flatulence.tw.
- 111 flatus.tw.
- 112 meteorism.tw.
- 113 Irritable bowel syndrome/
- 114 (irritable adj4 bowel adj4 syndrome).tw.
- 115 ibs.tw.
- 116 Vomiting/
- 117 Nausea/
- 118 (nausea or vomit\*).tw.
- 119 emesis.tw.
- 120 Fatigue/
- 121 Lethargy/
- 122 (malaise or fatigue or letharg\* or exhaust\*).tw.
- 123 exp Weight loss/
- 124 (weight adj4 los\*).tw.
- 125 (weight adj4 reduc\*).tw.
- 126 malnutrition.tw.
- 127 emaciat\*.tw.
- 128 Anorexia/
- 129 anorexia.tw.
- 130 Stomatitis, Aphthous/
- 131 (aphthous adj4 (stomatitis or stomatitides)).tw.
- 132 (aphthous adj4 ulcer\*).tw.
- 133 aphthae.tw.
- 134 (canker adj4 sore\*).tw.
- 135 Oral Ulcer/
- 136 (oral adj4 ulcer\*).tw.
- 137 (mouth adj4 ulcer\*).tw.
- 138 Anemia, Iron-Deficiency/
- 139 (iron adj4 deficien\*).tw.
- 140 (vitamin adj4 (k or d) adj4 deficien\*).tw.
- 141 Peripheral Nervous System Diseases/
- 142 peripheral neuropath\*.tw.
- 143 (peripheral adj4 nerv\* adj4 disease\*).tw.
- 144 (pns adj4 disease\*).tw.

**Medline Strategy, searched 24th July 2013 – 28th August 2014****Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>****Search Strategy:**

- 145 (Peripheral adj4 (oedema or edema)).tw.
- 146 exp Ataxia/
- 147 (ataxia\* or (machado adj4 joseph) or (narp adj4 syndrome) or (olivopontocerebellar adj4 atrophy) or (spinocerebellar adj4 degeneration) or (hippel adj4 lindau) or (incoordination\* or inco-ordination\* or dyscoordination\* or dysco-ordination\* or dyssynergia or dys-synergia) or (coordination adj4 lack\*) or (co-ordination adj4 lack\*) or (coordination adj4 impair\*) or (co-ordination adj4 impair\*) or (rubral adj4 tremor\*)).tw.
- 148 Infertility/
- 149 Infertility, Male/
- 150 Infertility, Female/
- 151 (infertility or subfertility or sub-fertility or sterility).tw.
- 152 (reduc\* adj4 fertility).tw.
- 153 (recurrent adj4 miscar\*).tw.
- 154 Growth Disorders/
- 155 Failure to thrive/
- 156 (fail\* adj4 thrive\*).tw.
- 157 (cerebrospinal adj4 degeneration\*).tw.
- 158 (short adj stature).tw.
- 159 (growth adj4 disorder\*).tw.
- 160 Osteoporosis/
- 161 (osteoporosis or osteoporoses).tw.
- 162 osteopenia.tw.
- 163 Osteomalacia/
- 164 osteomalacia\*.tw.
- 165 Puberty, Delayed/
- 166 (delayed adj4 puberty).tw.
- 167 Headache/
- 168 Headache disorders/
- 169 (headache\* or migraine).tw.
- 170 exp Epilepsy/
- 171 (epilep\* or seizure\*).tw.
- 172 Depression/
- 173 (depression\* or depressive\* or anxiet\* or melanchol\* or dysphoria or dysthymia or bipolar or bi-polar).tw.
- 174 Anxiety/
- 175 Anxiety Disorders/
- 176 (enamel adj4 defect\*).tw.
- 177 (tooth adj4 discoloration).tw.
- 178 (tooth adj4 discolouration).tw.
- 179 (arthriti\* or (still\* adj4 disease) or (felty adj4 syndrome) or (rheumatoid adj4 nodule)).tw.
- 180 exp Rheumatoid Arthritis/
- 181 "Signs and Symptoms"/
- 182 ((sign or signs) adj6 symptom\*).tw.
- 183 Risk Factors/
- 184 factor\*.tw.
- 185 predict\*.tw.
- 186 or/97-185
- 187 10 and 186
- 188 Liver/en [Enzymology]
- 189 Liver Diseases/en [Enzymology]

**Medline Strategy, searched 24th July 2013 – 28th August 2014****Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>****Search Strategy:**

- 190 ((abnormal\* or dysfunction\*) adj4 liver\*).tw.  
 191 ((elevat\* or high\* or raise\*) adj4 liver\*).tw.  
 192 Amenorrhea/  
 193 Oligomenorrhea/  
 194 (amenorrhea\* or amenorrhoea\* or oligomenorrhea\* or oligomenorrhoea\*).tw.  
 195 Menstruation Disturbances/  
 196 ((absen\* or cease\* or stop\*) adj4 (period\* or menstruat\* or menses)).tw.  
 197 hyposplen\*.tw.  
 198 splenic diseases/  
 199 spleen/  
 200 spleen\*.tw.  
 201 (gluten adj4 (sensitiv\* or neuropath\*)).tw.  
 202 exp Calcinosis/ and exp brain/  
 203 ((calcinos\* or calcificat\* or calcium\*) adj4 (brain\* or intracerebr\* or intracran\* or cerebr\*)).tw.  
 204 Intussusception/  
 205 (intestin\* adj4 (obstruct\* or invaginat\*)).tw.  
 206 (intussuscept\* or intususcept\*).tw.  
 207 Intestine Lymphoma/  
 208 Lymphoma/  
 209 lymphom\*.tw.  
 210 207 or 208  
 211 exp Intestines/  
 212 (intestin\* or bowel or gut).tw.  
 213 (gastrointestin\* adj4 tract).tw.  
 214 or/210-212  
 215 209 and 213  
 216 Esophageal Neoplasms/  
 217 ((oesophag\* or esophag\*) adj4 (neoplasm\* or cancer\* or carcinoma\* or adenocarcinom\* or tumour\* or tumor\* or malignan\* or metastas\* or lesion\*)).tw.  
 218 exp Colonic Neoplasms/  
 219 ((colon\* or sigmoid\*) adj4 (neoplasm\* or cancer\* or carcinoma\* or adenocarcinom\* or tumour\* or tumor\* or malignan\* or metastas\* or lesion\*)).tw.  
 220 (Gardner\* adj4 syndrome\*).tw.  
 221 (polypos\* adj4 (col\* or intestin\*)).tw.  
 222 exp anemia/  
 223 (anaemia\* or anemia\*).tw.  
 224 (ulcer\* adj4 jejun\*).tw.  
 225 exp Jejunal Diseases/  
 226 ((inflam\* or lesion\*) adj4 jejun\*).tw.  
 227 refractor\*.tw.  
 228 (unrespon\* or non-respon\* or nonrespon\* or non respon\*).tw.  
 229 (fail\* adj4 respon\*).tw.  
 230 ((ongoing or recur\*) adj4 symptom\*).tw.  
 231 exp Fractures, bone/  
 232 fractur\*.tw.  
 233 (bone\* adj4 (mineral\* or densit\* or soft\* or decay\*)).tw.  
 234 Vitamin D Deficiency/  
 235 avitaminosis D.tw.  
 236 ((calciferol or cholecalciferol or colecalciferol or egocalciferol) adj4 deficien\*).tw.

**Medline Strategy, searched 24th July 2013 – 28th August 2014****Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>****Search Strategy:**

- 237 Vitamin B 12 Deficiency/  
 238 Folic Acid Deficiency/  
 239 ((folic\* or folat\* or cyanocobalamin or vitamin\*) adj4 defici\*).tw.  
 240 Myocarditis/im [Immunology]  
 241 Myocardium/im [Immunology]  
 242 (autoimmune adj4 myocarditis).tw.  
 243 exp Bipolar Disorder/  
 244 (bipolar or mania\*).tw.  
 245 ((manic or depressive) adj4 (state\* or episod\* or psychos?s or disorder\* or syndrom\* or depression\* or illness\* or reaction\*)).tw.  
 246 Cardiomyopathies/  
 247 Cardiomyopathy, dilated/  
 247 cardiomyopath\*.tw.  
 249 myocardiopath\*.tw.  
 250 (myocardial\* adj4 disease\*).tw.  
 251 (heart adj4 myopath\*).tw.  
 252 (heart adj4 muscle adj4 disease\*).tw.  
 253 (cardiac adj4 muscle adj4 disease\*).tw.  
 254 (myocardial adj4 muscle adj4 disease\*).tw.  
 255 (deteriorat\* adj4 ((myocardium or heart or cardiac) adj4 muscle)).tw.  
 256 exp Purpura, Thrombocytopenic/  
 257 (thrombocytopen\* adj4 purpura\*).tw.  
 258 Dermatitis Herpetiformis/  
 259 (dermatitis adj4 herpetiformis).tw.  
 260 ((duhring\* or duehring\* or duhrig\* or duehrig\*) adj4 (dermatit\* or disease\* or brocq\* or brock\* or morbus\*)).tw.  
 261 (zosteriform adj4 erupt\*).tw.  
 262 (hidroa or hydroa).tw.  
 263 exp HIV/  
 264 exp HIV Infections/  
 265 (HIV or AIDS).tw.  
 266 (acquired adj4 immunodeficien\* adj4 syndrome\*).tw.  
 267 (human adj4 immunodeficien\* adj4 virus\*).tw.  
 268 (lymphadenopath\* adj4 assoc\* adj4 virus\*).tw.  
 269 (lav-htlv-iii or lav htlv iii).tw.  
 270 (htlv-III or htlv iii).tw.  
 271 (human\* adj4 t?cell\* adj4 leuk?emia\*).tw.  
 272 (human\* adj4 t?cell\* adj4 lymphotrop\*).tw.  
 273 exp Colitis, Microscopic/  
 274 ((microscop\* or collagen\* or lymphoc\*) adj4 colitis\*).tw.  
 275 Liver Cirrhosis, Biliary/  
 276 ((biliar\* or liver\*) adj4 cirrhos\*).tw.  
 277 exp Sarcoidosis/  
 278 sarcoidos\*.tw.  
 279 ((besnier\* or boeck\* or schaumann\* or heerfordt\* or Jungling\*) adj4 (syndrome\* or disease\* or sarcoid\*)).tw.  
 280 (lupus adj4 pernio).tw.  
 281 (lymphogranuloma adj4 benignum).tw.  
 282 neurosarcoidosis.tw.  
 283 (sarcoid\* adj4 granulome).tw.



**Medline Strategy, searched 24th July 2013 – 28th August 2014****Database: Ovid MEDLINE(R) <1946 to July Week 2 2013>****Search Strategy:**

284 (uveo adj4 parotid adj4 fever\*).tw.  
 285 (uveoparotid adj4 fever\*).tw.  
 286 or/188-207  
 287 or/215-285  
 288 286 or 287  
 289 10 and 288  
 290 36 or 60 or 98 or 187 or 289  
 291 animals/ not humans/  
 292 290 not 291  
 293 limit 292 to english language

&lt;Insert Note here&gt;

**A.2.2 Search strategy review question 4.4**

Should active case-finding be implemented in people with co-existing conditions/subgroups that are associated with an increased risk of coeliac disease?

**Table 2: search strategy 4.4****Medline Strategy, searched 28th July 2014****Database: Ovid MEDLINE(R) <1946 to July Week 3 2014>****Search Strategy:**

1 (coeliac adj4 disease).tw.  
 2 (celiac adj4 disease).tw.  
 3 (coeliac adj4 sprue).tw.  
 4 (celiac adj4 sprue).tw.  
 5 ((nontropical or non tropical) adj4 sprue).tw.  
 6 ((celiac or coeliac) adj4 syndrome).tw.  
 7 (gluten adj4 (enteropath\$ or sensitiv\$ or hypersensitiv\$ or intoleran\$)).tw.  
 8 ((glutenin or gliadin) adj4 (sensitiv\$ or hypersensitiv\$ or intoleran\$)).tw.  
 9 Celiac Disease/  
 10 or/1-9  
 11 Mass Screening/  
 12 exp Population Surveillance/  
 13 Case Management/  
 14 Diagnostic Tests, Routine/  
 15 (case\* adj4 (find\* or manage\*)).tw.  
 16 (active\* adj4 screen\*).tw.  
 17 ((routin\* or target\* or population\*) adj4 (screen\* or detect\* or surveill\*)).tw.  
 18 ((find\* or case\*) adj4 (undiagnos\* or undetect\*)).tw.  
 19 ((active\* or screen\* or early or proactiv\*) adj4 (detect\* or investigat\*)).tw.  
 20 early diagnosis/  
 21 (early adj4 diagnos\*).tw.  
 22 or/11-21  
 23 10 and 22  
 24 animals/ not humans/  
 25 23 not 24  
 26 limit 25 to english language

&lt;Insert Note here&gt;

### A.2.3 Search strategy review questions 5.1 & 5.2

#### Review 5.1

- a) What is the sensitivity and specificity of the serological tests for coeliac disease?
- b) Are the sensitivity and specificity results different in any specified subgroups?

#### Review 5.2

- a) Which serological test is the most appropriate to diagnose coeliac disease?
- b) Depending on test results, should more than one test be used and, if so, what should be the sequence of testing?
- c) Following which sequence of tests and test results is it appropriate to refer onwards for endoscopic intestinal biopsy for confirmatory diagnosis?

**Table 3: search strategy 5.1 & 5.2**

Medline Strategy, searched 11th October 2013	
Database: Ovid MEDLINE(R) <1946 to September Week 4 2013>	
Search Strategy:	
1	(coeliac adj4 disease).tw.
2	(celiac adj4 disease).tw.
3	(coeliac adj4 sprue).tw.
4	(celiac adj4 sprue).tw.
5	((nontropical or non tropical) adj4 sprue).tw.
6	((celiac or coeliac) adj4 syndrome).tw.
7	(gluten adj4 (enteropath* or sensitive* or hypersensitive* or intoleran*)).tw.
8	((glutenin or gliadin) adj4 (sensitive* or hypersensitive* or intoleran*)).tw.
9	Celiac Disease/
10	or/1-9
11	(endomysi* adj4 antibod*).tw.
12	(immunoglobulin adj4 endomysi*).tw.
13	((anti-endomysi* or antiendomysi* or anti endomysi*) adj antibody*).tw.
14	((iga or igg) adj4 endomysi*).tw.
15	((iga or igg) adj4 (anti-endomysi* or antiendomysi* or anti endomysi*)).tw.
16	(immunoglobulin adj4 (anti-endomysi* or antiendomysi* or anti endomysi*)).tw.
17	(iga-ema or igg-ema).tw.
18	ema.tw.
19	or/11-18
20	10 and 19
21	(transglutaminase adj4 antibod*).tw.
22	(tissue adj4 transglutaminase adj4 antibod*).tw.
23	((anti-tissue or antitissue or anti tissue) adj4 transglutaminase) and antibody*).tw.
24	(immunoglobulin adj4 transglutaminase).tw.
25	((iga or igg) adj4 transglutaminase).tw.
26	(anti-httg or anti-htg).tw.
27	((anti-human or antihuman or anti human) adj4 transglutaminase adj4 antibod*).tw.
28	transglutaminases/
29	tTG.tw.
30	or/21-29
31	10 and 30

**Medline Strategy, searched 11th October 2013****Database: Ovid MEDLINE(R) <1946 to September Week 4 2013>****Search Strategy:**

32 (gliadin adj4 antibod\*).tw.  
 33 (immunoglobulin adj4 gliadin).tw.  
 34 ((antigliadin or anti-gliadin or anti gliadin) adj4 antibod\*).tw.  
 35 ((igg or iga) adj4 gliadin).tw.  
 36 ((igg or iga) adj4 (antigliadin or anti-gliadin or anti gliadin)).tw.  
 37 (immunoglobulin adj4 (antigliadin or anti-gliadin or anti gliadin)).tw.  
 38 (elisa adj4 test\*).tw.  
 39 Gliadin/ and Immunoglobulins/  
 40 AGA.tw.  
 41 or/32-40  
 42 10 and 41  
 43 (human adj4 (leukocyte\* or leucocyte\*) adj4 antigen\*).tw.  
 44 (hla adj4 typ\*).tw.  
 45 (dr3 adj4 dq2).tw.  
 46 (dr4 adj4 dq8).tw.  
 47 (hla adj4 dq2).tw.  
 48 (hla adj4 dq8).tw.  
 49 HLA-DQ Antigens/  
 50 HLA-DR3 Antigen/  
 51 or/43-50  
 52 10 and 51  
 53 Serologic Tests/  
 54 (serologic adj4 test\*).tw.  
 55 53 or 54  
 56 10 and 55  
 57 20 or 31 or 42 or 52 or 56  
 58 animals/ not humans/  
 59 57 not 58  
 60 limit 59 to english language

&lt;Insert Note here&gt;

**A.2.4 Search strategy review question 5.3**

What are the referral indications for endoscopic intestinal biopsy for further investigation in people with coeliac disease?

**Table 4: search strategy 5.3****Medline Strategy, searched 17th April 2014****Database: Ovid MEDLINE(R) <1946 to April Week 2 2014>****Search Strategy:**

1 (coeliac adj4 disease).tw.  
 2 (celiac adj4 disease).tw.  
 3 (coeliac adj4 sprue).tw.  
 4 (celiac adj4 sprue).tw.  
 5 ((nontropical or non tropical) adj4 sprue).tw.

**Medline Strategy, searched 17th April 2014****Database: Ovid MEDLINE(R) <1946 to April Week 2 2014>****Search Strategy:**

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6 ((celiac or coeliac) adj4 syndrome).tw.
7 (gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8 ((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9 Celiac Disease/
10 or/1-9
11 Biopsy/
12 Biopsy Needle/
13 exp Image-Guided Biopsy/
14 biops*.tw.
15 or/11-14
16 exp Intestines/
17 intestin*.tw.
18 Duodenum/
19 (duodenum or duodenal).tw.
20 or/16-19
21 10 and 15 and 20
22 Endoscopy/
23 (endoscop* or scope*).tw.
24 Endoscopy, Gastrointestinal/
25 Capsule Endoscopy/
26 Duodenoscopy/
27 duodenoscop*.tw.
28 Gastroscopy/
29 gastroscop*.tw.
30 Esophagoscopy/
31 (esophagoscop* or oesophagoscop*).tw.
32 Endoscopy, Digestive System/
33 (esophagogastroduendoscop* or oesophagogastroduendoscop*).tw.
34 or/22-33
35 "Referral and Consultation"/
36 (refer or referr* or consult* or second opinion* or gatekeep*).tw.
37 35 or 36
38 21 and 34
39 21 and 37
40 38 or 39
41 animals/ not humans/
42 40 not 41
43 limit 42 to english language

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&lt;Insert Note here&gt;

**A.2.5 Search strategy review question 5.4**

- a) How frequently should people with coeliac disease be routinely monitored?
- b) Should the frequency of routine monitoring differ for patients with at risk of developing certain complications?

c) What should routine monitoring consist of?

**Table 5: Search strategy 5.4**

Medline Strategy, searched 6th March 2014	
Database: Ovid MEDLINE(R) <1946 to February Week 4 2014>	
Search Strategy:	
1	(coeliac adj4 disease).tw.
2	(celiac adj4 disease).tw.
3	(coeliac adj4 sprue).tw.
4	(celiac adj4 sprue).tw.
5	((nontropical or non tropical) adj4 sprue).tw.
6	((celiac or coeliac) adj4 syndrome).tw.
7	(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8	((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9	Celiac Disease/
10	or/1-9
11	Long-Term Care/
12	"Continuity of Patient Care"/
13	exp Patient Care Planning/
14	Disease Management/
15	Patient Compliance/
16	(patient adj4 (compliance or non-compliance or noncompliance or adherence or non-adherence or nonadherence or cooperation or co-operation)).tw. (12335)
17	lost to follow-up/
18	((long-term or long term or longterm or life-long or life long or lifelong or active or adequa* or continu* or frequen* or repeat* or routine* or regular* or histolog* or serolog* or recommend* or length* or timing or time or number or continuity or continuum or optim* or plan or planned or planning) adj4 (followup* or follow-up* or follow up* or assess* or practice* or strateg* or review* or care or manag*)).tw.
19	monitor*.tw.
20	time factors/
21	or/11-20
22	10 and 21
23	Bone Density/
24	Osteoporosis/
25	exp "Bone and Bones"/
26	(bone* or osteoporo*).tw.
27	or/23-26
28	Serology/
29	exp Serologic Tests/
30	(serolog* or serodiagnos*).tw.
31	or/28-30
32	Histology/
33	histolog*.tw.
34	32 or 33
35	exp Histological Techniques/
36	Diet/
37	Diet, Gluten-Free/
38	exp Nutrition Therapy/
39	(diet* or nutrit*).tw.
40	or/35-39

**Medline Strategy, searched 6th March 2014****Database: Ovid MEDLINE(R) <1946 to February Week 4 2014>****Search Strategy:**

41 (symptom\* adj4 response\*).tw.  
 42 27 or 31 or 34 or 40 or 41  
 43 (followup\* or follow-up\* or follow up\* or assess\* or practice\* or strateg\* or review\* or care or manag\*).tw.  
 44 42 and 43  
 45 10 and 44  
 46 22 or 45  
 47 animals/ not humans/  
 48 46 not 47  
 49 limit 48 to english language

&lt;Insert Note here&gt;

**A.2.6 Search strategy review question 6.1**

- a.) What are the potential causes of non-responsive coeliac disease?  
 b.) In patients with confirmed refractory coeliac disease what investigative procedures should be undertaken, such as:
- Clonality assessment
  - Flow cytometry
  - Aberrant T cell assessment
  - Immunophenotyping
  - Imaging

**Table 6: search strategy 6.1****Medline Strategy, searched 22nd April 2014****Database: Ovid MEDLINE(R) <1946 to April Week 2 2014>****Search Strategy:**

1 (coeliac adj4 disease).tw.  
 2 (celiac adj4 disease).tw.  
 3 (coeliac adj4 sprue).tw.  
 4 (celiac adj4 sprue).tw.  
 5 ((nontropical or non tropical) adj4 sprue).tw.  
 6 ((celiac or coeliac) adj4 syndrome).tw.  
 7 (gluten adj4 (enteropath\* or sensitiv\* or hypersensitiv\* or intoleran\*)).tw.  
 8 ((glutenin or gliadin) adj4 (sensitiv\* or hypersensitiv\* or intoleran\*)).tw.  
 9 Celiac Disease/  
 10 or/1-9  
 11 refractor\*.tw.  
 12 (unrespon\* or non-respon\* or nonrespon\* or non respon\*).tw.  
 13 (fail\* adj4 respon\*).tw.  
 14 ((ongoing or recur\*) adj4 symptom\*).tw.  
 15 ((villous\* or villus\* or villi\* or microvilli\* or microvillus\* or microvillous\*) adj4 atroph\*).tw.  
 16 or/11-15  
 17 Microvilli/

**Medline Strategy, searched 22nd April 2014**  
**Database: Ovid MEDLINE(R) <1946 to April Week 2 2014>**  
**Search Strategy:**

- 18 Atrophy/
- 19 17 and 18
- 20 16 or 19
- 21 10 and 20
- 22 animals/ not humans/
- 23 21 not 22
- 24 limit 23 to english language

<Insert Note here>

## A.2.7 Search strategy review question 6.2

What is the effectiveness of pharmacological treatments for people with refractory coeliac disease?

**Table 7: search strategy 6.2**

**Medline Strategy, searched 14th June 2014**  
**Database: Ovid MEDLINE(R) <1946 to June Week 1 2013>**  
**Search Strategy:**

- 1 Celiac Disease/
- 2 ((coeliac\* or celiac\*) adj4 disease).tw.
- 3 ((coeliac\* or celiac\*) adj4 sprue).tw.
- 4 ((nontropical or non tropical) adj4 sprue).tw.
- 5 ((coeliac\* or celiac\*) adj4 syndrome).tw.
- 6 (gluten adj4 (enteropath\* or sensitiv\* or hypersensitiv\* or intoleran\*)).tw.
- 7 ((glutenin or gliadin) adj4 (sensitiv\* or hypersensitiv\* or intoleran\*)).tw.
- 8 or/1-7
- 9 Beclomethasone/ or (beclomethason\* or beclametason\* or beclometason\*).tw.
- 10 Betamethasone/ or betamethason\*.tw.
- 11 Budesonide/ or budesonid\*.tw.
- 12 Ciclesonide/ or ciclesonid\*.tw.
- 13 Adrenocorticotrophic Hormone/
- 14 (adrenocorticotrop\* adj4 hormone\*).tw.
- 15 Corticotropin\*.tw.
- 16 Cortisone/ or cortison\*.tw.
- 17 Deflazacort\*.tw.
- 18 Dexamethasone/ or dexamethason\*.tw.
- 19 Fludrocortisone/ or fludrocortison\*.tw.
- 20 flunisolid\*.tw.
- 21 Hydrocortisone/ or hydrocortison\*.tw.
- 22 Methylprednisolone/ or Methylprednisolon\*.tw.
- 23 Mometasone Furoat\*.tw.
- 24 Prednisolone/
- 25 prednisolon\*.tw.
- 26 Prednisone/ or prednison\*.tw.
- 27 Cosyntropin/ or (Tetracosactid\* or cosyntropin\*).tw.

**Medline Strategy, searched 14th June 2014****Database: Ovid MEDLINE(R) <1946 to June Week 1 2013>****Search Strategy:**

- 28 Triamcinolone/ or Triamcinolon\*.tw.
- 29 Cyclosporine/ or (cyclosporin\* or ciclosporin\*).tw.
- 30 Azathioprine/ or (azathioprin\* or azatioprin\*).tw.
- 31 infliximab\*.tw.
- 32 adalumimab\*.tw.
- 33 etanercept\*.tw.
- 34 golimumab\*.tw.
- 35 certolizumab\*.tw.
- 36 Cladribine/ or cladribin\*.tw.
- 37 (ASA adj4 preparation\*).tw.
- 38 Mesalamine/ or (mesalamin\* or mesalazin\*).tw.
- 39 alemtuzumab\*.tw.
- 40 thioguanine/ or (thioguanin\* or tioguanin\*).tw.
- 41 Immunosuppressive Agents/
- 42 (immunosuppress\* adj4 (antiproliferative\* or agent\* or substance\* or drug\*)).tw.
- 43 (immun\* adj4 suppress\*).tw.
- 44 Anti-Inflammatory Agents, Non-Steroidal/
- 45 (steroid\* or non-steroid\* or nonsteroid\* or NSAID\*).tw.
- 46 Antibodies, Monoclonal/
- 47 ((antibod\* adj4 monoclonal\*) or anti-tnf\*).tw.
- 48 Antimetabolites/
- 49 Antimetabolites, Antineoplastic/
- 50 antimetaboli\*.tw.
- 51 Antineoplastic Agents/
- 52 ((antineoplast\* or anti-cancer\* or anticancer\*) adj4 (drug\* or agent\*)).tw.
- 53 ((tumour\* or tumor\*) adj4 inhibit\*).tw.
- 54 adrenal cortex hormones/
- 55 glucocorticoids/
- 56 glucocort\*.tw.
- 57 (adrenal adj4 cortex\* adj4 hormon\*).tw.
- 58 (corticosteroid\* or corticoid\*).tw.
- 59 or/9-58
- 60 8 and 59
- 61 animals/ not humans/
- 62 60 not 61
- 63 limit 62 to english language

*<Insert Note here>***A.2.8 Search strategy review question 6.3**

What is the effectiveness of nutritional management or nutritional support for people with refractory coeliac disease?



**Table 8: search strategy 6.3**

Medline Strategy, searched /13th November 2013	
Database: Ovid MEDLINE(R) <1946 to October Week 5 2013>	
Search Strategy:	
1	(coeliac adj4 disease).tw.
2	(celiac adj4 disease).tw.
3	(coeliac adj4 sprue).tw.
4	(celiac adj4 sprue).tw.
5	((nontropical or non tropical) adj4 sprue).tw.
6	((celiac or coeliac) adj4 syndrome).tw.
7	(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8	((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9	Celiac Disease/
10	or/1-9
11	Diet/
12	((diet* or food* or nutrition*) adj4 (exclus* or exclud* or restrict* or support* or eliminat*)).tw.
13	Functional Food/
14	Food, Fortified/
15	(food* adj4 (fortif* or enrich* or additiv* or supplement*)).tw.
16	Feeding Method/
17	feed*.tw.
18	Enteral Nutrition/
19	((enteral* or enteric* or intragastric or intestinal or intrainstestinal or oral* or sip or tube or force or gastric) adj4 nutrition*).tw.
20	((nasogastric* or gastronomy or jejuostomy) adj4 tube*).tw.
21	exp Parenteral Nutrition/
22	((parenter* or intraven* or hyperalimentation or alimentation or fluid) adj4 nutrition*).tw.
23	exp Food Hypersensitivity/
24	((egg* or milk or nut or nuts or peanut* or groundnut* or wheat* or soya or fish or shellfish or crustacean* or mollusc* or sesame or soybean or celery or mustard or lupin or sulphur dioxide or food* or nutrition* or diet*) adj4 (hypersensitiv* or allerg*)).tw.
25	Energy Intake/
26	((nutrition* or food* or diet* or energy or calorie* or caloric) adj4 (intak* or ingest* or uptak* or consum* or method*)).tw.
27	(appetite adj4 regulat*).tw.
28	or/11-27
29	10 and 28
30	animals/ not humans/
31	29 not 30
32	limit 31 to english language

<Insert Note here>

## A.2.9 Search strategy review question 6.4

What is the effectiveness of autologous stem cell transplant for people with refractory coeliac disease?

**Table 9: search strategy 6.4**

Medline Strategy, searched 4th June 2013	
Database: Ovid MEDLINE(R) <1946 to May Week 4 2013>	
Search Strategy:	
1	Celiac Disease/
2	(coeliac* or celiac*).tw.
3	((nontropical or non tropical) adj4 sprue).tw.
4	(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
5	((gluterin or gliadin) adj4 (sensitiv* or hypersensitivi* or intoleran*)).tw.
6	Enteropathy-Associated T-Cell Lymphoma/
7	(enteropath* adj4 associat* adj4 T adj4 cell* adj4 lymphom*).tw.
8	EATL.tw.
9	or/1-8
10	Hematopoietic Stem Cell Transplantation/
11	((hematopiet* or hemoatopoet* or haematopiet* or haemoatopoet* or autolog* or allogene*) adj4 (stem or cell* or transplant* or transfer* or treat*)).tw.
12	Auto-SCT.tw.
13	((stem adj4 cell*) and (support* or transfer* or transplant* or treat*)).tw.
14	autotransplant*.tw.
15	autograft*.tw.
16	ASCT.tw.
17	HSCT.tw.
18	or/10-17
19	hematopoietic stem cells/
20	((hematopiet* or hematopoet* or haematopiet* or haemoatopoet*) adj4 cell*).tw.
21	19 or 20
22	Transplantation/
23	Stem Cell Transplantation/
24	Transplants/
25	Cell Transplantation/
26	(transfer* or transplant* or graft*).tw.
27	or/22-26
28	21 and 27
29	18 or 28
30	exp drug therapy/
31	chemo*.tw.
32	30 or 31
33	29 or 32
34	9 and 33
35	animals/ not Humans/
36	34 not 35
37	limit 36 to english language

<Insert Note here>

## A.2.10 Search strategy review questions 7.1 & 7.2

### Review 7.1

- a) What information do people (and their family members or carers, as appropriate) need to help them decide whether to undergo initial testing for coeliac disease?

- b) If people are to undergo initial testing, what dietary information do they (or their family members or carers) need before testing to ensure that test results are as accurate as possible?

## Review 7.2

- a) What information, education and support do people with coeliac disease (and their family members or carers, as appropriate) need to improve adherence to a gluten-free diet and self-management of their condition?
- b) What is the patient perspective of self-management and how to improve adherence, including what information is required, different monitoring strategies, and with whom they are followed up?

**Table 10: search strategy 7.1 & 7.2**

Medline Strategy, searched 8th May 2014	
Database: Ovid MEDLINE(R) <1946 to April Week 5 2014>	
Search Strategy:	
1	(coeliac adj4 disease).tw.
2	(celiac adj4 disease).tw.
3	(coeliac adj4 sprue).tw.
4	(celiac adj4 sprue).tw.
5	((nontropical or non tropical) adj4 sprue).tw.
6	((celiac or coeliac) adj4 syndrome).tw.
7	(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8	((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9	Celiac Disease/
10	or/1-9
11	Qualitative Research/
12	Nursing Methodology Research/
13	exp Interviews as topic/
14	Questionnaires/
15	Narration/
16	Health Care Surveys/
17	(qualitative* or interview* or focus group* or questionnaire* or narrative* or narration* or survey*).tw.
18	(ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or thematic* adj4 analys*) or theoretical sampl* or purposive sampl*).tw.
19	(hermeneutic* or heidegger* or husser* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).tw.
20	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them*).tw.
21	or/11-20
22	exp Patients/px
23	exp Family/px
24	Caregivers/px
25	((patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or husband* or wife* or wive* or partner* or mother* or father* or sibling* or sister* or brother* or inpatient* or in-patient*) adj6 (experience* or belief* or stress* or emotion* or anx* or fear* or concern* or uncertain* or unsure or thought* or feeling* or felt* or view* or opinion* or perception* or perspective* or attitud* or satisfact* or know* or understand* or aware*)).ti.
26	Stress, Psychological/
27	Adaptation, psychological/
28	Emotions/
29	Anxiety/

**Medline Strategy, searched 8th May 2014****Database: Ovid MEDLINE(R) <1946 to April Week 5 2014>****Search Strategy:**

```

30  Fear/
31  exp Consumer Satisfaction/
32  patient* report* outcome*.tw.
33  or/22-32
34  exp Patients/
35  exp Family/
36  Caregivers/
37  (patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or
husband* or wife* or wive* or partner* or mother* or father* or sibling* or sister* or brother* or
inpatient* or in-patient*).ti.
38  or/34-37
39  Pamphlets/
40  Needs Assessment/
41  Information Centers/
42  Information Services/
43  Health Education/
44  Information Dissemination/
45  Counseling/
46  Social Support/
47  Self-Help Groups/
48  Self Care/
49  ((patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or
husband* or wife* or wive* or partner*) adj6 (educat* or informat* or communicat* or pamphlet* or
handout* or hand-out* or hand out* or booklet* or leaflet* or support* or need* or advice* or
advis*).ti.
50  ((patient* or parent* or famil* or relative* or carer* or caregiver* or care-giver* or spous* or
husband* or wife* or wive* or partner*) adj6 (counsel* or selfhelp* or self-help* or self help* or
selfcar* or self-car* or self car*).ti.
51  Patient Education as Topic/
52  Patient Education Handout/
53  Consumer Health Information/
54  patient* diar*.tw.
55  or/39-54
56  38 and 55
57  21 or 33 or 56
58  Animals/ not Humans/
59  57 not 58
60  10 and 59
61  animals/ not humans/
62  60 not 61
63  limit 62 to english language

```

*<Insert Note here>***A.2.11 Search strategy review question 7.3**

What dietary management strategy/advice should be given to people with coeliac disease?

Should the advice include avoiding gluten-free oats as part of the exclusion diet?

**Table 11: search strategy 7.3**

<b>Medline Strategy, searched 15th November 2013</b>	
<b>Database: Ovid MEDLINE(R) &lt;1946 to November Week 1 2013&gt;</b>	
<b>Search Strategy:</b>	
1	(coeliac adj4 disease).tw.
2	(celiac adj4 disease).tw.
3	(coeliac adj4 sprue).tw.
4	(celiac adj4 sprue).tw.
5	((nontropical or non tropical) adj4 sprue).tw.
6	((celiac or coeliac) adj4 syndrome).tw.
7	(gluten adj4 (enteropath* or sensitiv* or hypersensitiv* or intoleran*)).tw.
8	((glutenin or gliadin) adj4 (sensitiv* or hypersensitiv* or intoleran*)).tw.
9	Celiac Disease/
10	or/1-9
11	Diet/
12	Dietary Supplements/
13	((supplement* or additiv* or fortif*) adj4 (food* or diet* or nutrition*)).tw.
14	(nutr?ceutical* or neutr?ceutical*).tw.
15	((nutrition* or diet* or food*) adj4 (manag* or advic* or guid* or support* or strateg*)).tw.
16	Vitamins/
17	vitamin*.tw.
18	Vitamin B 12/
19	Vitamin B Complex/
20	Vitamin D/
21	Calcium/
22	calcium.tw.
23	Iron/
24	iron.tw.
25	Folic Acid/
26	(folic adj4 acid).tw.
27	(vit adj4 (m or b9 or b-9 or b 9)).tw.
28	(pteroylglutamic or folvite or folate or folacin).tw.
29	Avena Sativa/
30	(avena adj4 sativa).tw.
31	oat*.tw.
32	(cereal* or porridge* or muesli* or granola*).tw.
33	or/11-32
34	10 and 33 (2608)
35	animals/ not humans/
36	34 not 35
37	limit 36 to english language

<Insert Note here>

## A.3 Health economics search strategy

### A.3.1 Economic evaluations and quality of life data

#### Sources searched to identify economic evaluations

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

Search filters to retrieve economic evaluations and quality of life papers were appended to all of the search strategies **above (except 5.1, 5.2, 5.3, 7.1 and 7.2)** to identify relevant evidence between May 2013 and July 2014. The re-run searches took place in December 2014.

**Table 12: 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.	
Economic evaluations	
1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/
9	exp Models, Economic/
10	Markov Chains/
11	Monte Carlo Method/
12	Decision Trees/
13	econom\$.tw.
14	cba.tw.
15	cea.tw.
16	cua.tw.
17	markov\$.tw.
18	(monte adj carlo).tw.
19	(decision adj2 (tree\$ or analys\$)).tw.
20	(cost or costs or costing\$ or costly or costed).tw.
21	(price\$ or pricing\$).tw.
22	budget\$.tw.
23	expenditure\$.tw.
24	(value adj2 (money or monetary)).tw.
25	(pharmacoeconomic\$ or (pharmaco adj economic\$)).tw.
26	or/1-25
Quality of life	
1	"Value of Life"/
2	Quality-Adjusted Life Years/

**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.**

**Economic evaluations**

- 3 quality adjusted life.tw.
- 4 (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
- 5 disability adjusted life.tw.
- 6 daly\$.tw.
- 7 Health Status Indicators/  
 8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
- 9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
- 10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
- 11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
- 12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
- 13 (euroqol or euro qol or eq5d or eq 5d).tw.
- 14 (hye or hyes).tw.
- 15 health\$ year\$ equivalent\$.tw.
- 16 (health adj3 state adj3 utilit\$).tw.
- 17 (utilit\$ adj3 (health\$ or valu\$ or weight\$ or scor\$ or measure\$)).tw.
- 18 (hui or hui1 or hui2 or hui3).tw.
- 19 disutili\$.tw.
- 20 rosser.tw.
- 21 quality of wellbeing.tw.
- 22 quality of well-being.tw.
- 23 qwb.tw.
- 24 willingness to pay.tw.
- 25 standard gamble\$.tw.
- 26 time trade off.tw.
- 27 time tradeoff.tw.
- 28 tto.tw.
- 29 (preferen\$ weight\$ or health state preferen\$).tw.
- 30 or/1-30

<Insert Note here>

## A.4 Review protocols

### List of key clinical issues and review questions

Key clinical issue	Areas being included	Question	Not being included
Recognition (update)	Presenting features that raise suspicion of coeliac disease <ul style="list-style-type: none"> <li>• Signs and symptoms</li> <li>• Populations with increased risk of coeliac disease</li> <li>• Long term consequences of undiagnosed coeliac disease</li> </ul> Active case-finding	4.1 4.1 4.3 4.4	
Diagnosis and monitoring (update)	Accuracy of serological tests Sequencing of serological tests Referral indications for endoscopic intestinal biopsy Frequency of routine monitoring (and if it differs by risk) and different monitoring strategies	5.1 5.2 5.3 5.4	Self-diagnosis kits and point of care tests
Non-responsive and refractory coeliac disease	Diagnosis of non-responsive and refractory coeliac disease Pharmacological treatment Nutritional management Autologous stem cell transplant	6.1 6.2 6.3 6.4	
Information, education and support	Information provision prior to serological testing (update) Information about gluten-free diets and self-management Dietary management of people with coeliac disease	7.1 7.2 7.3	



	Details	Additional comments
<b>Review question 4.1, 4.2, 4.3</b>	<p>Which presenting features raise suspicion of coeliac disease?</p> <p>4.1 What are the clinical signs and symptoms which raise suspicion of coeliac disease?</p> <p>4.2 What populations have an increased risk of developing coeliac disease?</p> <ol style="list-style-type: none"> <li>i. Co-existing diseases</li> <li>ii. Other factors (ie. first-degree relatives)</li> </ol> <p>4.3 What are the long-term consequences of undiagnosed or untreated coeliac disease?</p>	
<b>Objectives</b>	To establish what presenting clinical features and conditions might i) raise suspicions about the presence of coeliac disease and possible need for further testing; ii) indicate subgroups who are at increased risk; iii) be associated with long-term consequences of undiagnosed coeliac disease	
<b>Type of review</b>	Diagnostic (4.1) epidemiological (4.2), and prognostic (4.3)	
<b>Language</b>	English only	
<b>Study design</b>	<p>No restriction (except qualitative studies and case reports)</p> <p>Case series are excluded for all but c.</p>	
<b>Status</b>	Published papers only (full text)	
<b>Population</b>	<p>Children, young people and adults with: 4.1. and 4.2. undiagnosed coeliac disease, untreated coeliac disease, including at the time of diagnosis (for 'other factors': a diagnosis of coeliac disease and families of patients with coeliac disease) 4.3. undiagnosed or untreated coeliac disease.</p> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Coeliac disease without biopsy confirmation (ie. determined from serological tests only) except for clinical signs and symptoms, rate in first-degree relatives and long-term consequences</li> <li>• Signs and symptoms of patients after diagnosis of coeliac disease unless untreated (since treatment is likely to alter signs and symptoms)</li> <li>• Rates of comorbidities that develop in patients after they have been diagnosed with coeliac disease</li> <li>• Long-term consequences in patients with diagnosed or untreated coeliac disease (ie. this does not give the 'true' natural history of coeliac as patients with diagnosed coeliac are likely to be receiving treatment)</li> </ul>	<p>The GDG agreed to exclude any studies which have not confirmed the diagnosis of coeliac with biopsy (including those studies which use serological tests only) because they were less confident in the ability of these tests to confirm coeliac disease.</p> <p>An exception to this was for clinical signs and symptoms (a), first degree relatives (bii), and long term consequences (c) where the GDG felt it was important to present studies which reported serological positivity only in addition to those that reported on biopsy-confirmed coeliac disease.</p> <p>The GDG felt rates confirmed on serological testing of anti-tTG and/or anti-EMA were appropriate and AGA only if it was used in conjunction with either anti-tTG or anti-EMA as it is known to result in high false positives.</p> <p>However, for examining first-degree relatives of patients with coeliac disease, they felt it was important that the index patient (or proband) had biopsy-confirmed coeliac disease.</p> <p>The GDG felt that excluding studies that did not report biopsy-confirmed coeliac disease would remove a large proportion of the relevant literature in these areas. However, they did feel it was important to present the results from biopsy-confirmed coeliac disease and serological positivity, separately.</p>

<b>Factors/ Variables/ Predictors</b>	<p>4.1. Presenting clinical features:</p> <ul style="list-style-type: none"> <li>• abnormal liver enzymes</li> <li>• amenorrhoea</li> <li>• chronic or intermittent diarrhoea/constipation</li> <li>• dental complications (enamel deterioration)</li> <li>• failure to thrive, faltering growth (in children) or delayed puberty</li> <li>• functional hyposplenism</li> <li>• gluten sensitive neuropathy</li> <li>• intra-cerebral calcification</li> <li>• intussusception (bowel telescopes within self )</li> <li>• malignancy including intestinal lymphoma, oesophageal cancer, colonic cancer</li> <li>• peripheral neuropathy</li> <li>• persistent or unexplained gastrointestinal symptoms including nausea and vomiting</li> <li>• pregnancy outcomes (sub-fertility, early miscarriage, intra-uterine growth retardation, premature babies)</li> <li>• prolonged fatigue</li> <li>• sudden or unexpected weight loss, height loss or fragility fractures</li> <li>• ulcerative jejunitis</li> <li>• unexplained iron-deficiency anaemia, or other unspecified anaemia</li> <li>• recurrent abdominal pain, cramping or distension</li> <li>• recurrent aphthous-ulceration</li> <li>• refractory coeliac disease</li> <li>• reduced bone mineral density</li> <li>• vitamin D, vitamin B12, folic acid and iron deficiency</li> </ul> <p>4.2. Coexisting conditions:</p> <ul style="list-style-type: none"> <li>• Addisons disease</li> <li>• all autoimmune diseases (such as autoimmune thyroid disease, autoimmune myocarditis, autoimmune hepatitis)</li> <li>• alopecia areata</li> <li>• bipolar disorder or depression</li> <li>• bone mineral disease (such as rickets or osteomalacia)</li> <li>• cardiomyopathy</li> <li>• chronic thrombocytopenia purpura</li> <li>• dermatitis herpetiformis</li> <li>• Downs syndrome</li> <li>• epilepsy</li> <li>• HIV</li> <li>• IgA deficiency</li> </ul>	
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	<ul style="list-style-type: none"> <li>• irritable bowel syndrome</li> <li>• juvenile idiopathic arthritis</li> <li>• microscopic colitis</li> <li>• neurological conditions (ataxia, headache, peripheral neuropathy)</li> <li>• osteoporosis (including fracture risk)</li> <li>• primary biliary cirrhosis</li> <li>• rheumatoid arthritis</li> <li>• sarcoidosis</li> <li>• Sjogren's syndrome</li> <li>• Turner syndrome</li> <li>• type 1 diabetes</li> <li>• Williams syndrome</li> </ul> <p>Other factors /specific subgroups:</p> <ul style="list-style-type: none"> <li>• first-degree relatives with coeliac disease</li> <li>• lower socioeconomic status</li> <li>• North African communities (specifically Berber communities)</li> </ul>	
<b>Comparator</b>	4.1 Confirmed diagnosis by intestinal biopsy only 4.2, 4.3 NA	
<b>Outcome measures</b>	<p>Specific for 4.1)</p> <ul style="list-style-type: none"> <li>• Accuracy metrics (sensitivity, specificity, +LR, -LR, PPV, NPV, etc.)</li> <li>• Predictive measures from adjusted regression model</li> </ul> <p>Specific for 4.2)</p> <ul style="list-style-type: none"> <li>• Risk of having coeliac disease</li> <li>• Risk of/event rates of complications</li> <li>• Growth in children and young people</li> </ul> <p>Specific for 4.3)</p> <ul style="list-style-type: none"> <li>• Complications of coeliac disease of</li> <li>• Complications from the long-term consequences</li> <li>• Growth in children and young people</li> </ul> <p>Overall:</p> <ul style="list-style-type: none"> <li>• Mortality</li> <li>• Resource use and cost</li> <li>• Health related quality of life</li> </ul>	
<b>Other criteria for inclusion / exclusion of studies</b>	<p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Case reports, case series (except for c), or qualitative studies</li> <li>• For long-term, consequences (c), studies with less than 50 patients</li> <li>• Non coeliac disease gluten sensitivity</li> <li>• Wheat allergy and sensitivity</li> </ul>	
<b>Search strategies</b>	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
<b>Review strategies</b>	Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.	

	All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.	
<b>Identified papers</b>	<p><u>Sample of papers identified in NICE CG86 for a):</u></p> <p>Bottaro G, Cataldo F, Rotolo N, et al. (1999) The clinical pattern of subclinical/silent celiac disease: an analysis on 1026 consecutive cases. <i>American Journal of Gastroenterology</i> 94: 691–6</p> <p>Emami MH (2008) Diagnostic accuracy of IgA anti-tissue transglutaminase in patients suspected of having coeliac disease in Iran. <i>Journal of Gastrointestinal and Liver Diseases</i> 17: 141–6</p> <p>Garampazzi A, Rapa A, Mura S, et al. (2007) Clinical pattern of celiac disease is still changing. <i>Journal of Pediatric Gastroenterology and Nutrition</i> 45: 611–4</p> <p>Vilppula A, Collin P, Maki M, et al. (2008) Undetected coeliac disease in the elderly: a biopsy-proven population-based study. <i>Digestive and Liver Disease</i> 40: 809–13</p> <p>Brandimarte G, Tursi A, Giorgetti GM (2002) Changing trends in clinical form of celiac disease. Which is now the main form of celiac disease in clinical practice? <i>Minerva Gastroenterologica e Dietologica</i> 48: 121–30</p> <p><u>Systematic Reviews for b):</u></p> <p><u>Dretzke J, Cummins C, Sandercock J, et al. (2004)</u> Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus. <i>Health Technology Assessment</i> 8(22):1-196</p> <p><u>Sample of papers identified by NICE CG86 for b):</u></p> <p>Salardi S, Volta U, Zucchini S, et al. (2008) Prevalence of celiac disease in children with type 1 diabetes mellitus increased in the mid-1990s: an 18-year longitudinal study based on anti-endomysial antibodies. <i>Journal of Pediatric Gastroenterology and Nutrition</i> 46: 612–4</p> <p>Leeds JS, Sanders DS (2007) Is there an association between coeliac disease and irritable bowel syndrome? <i>Gut</i> 56: 1326–7</p> <p>Guliter S, Yakaryilmaz F, Ozkurt Z, et al. (2007) Prevalence of coeliac disease in patients with autoimmune thyroiditis in a Turkish population. <i>World Journal of Gastroenterology</i> 13: 1599–601</p> <p>Goldacre MJ, Wotton CJ, Seagroatt V, et al. (2004) Cancers and immune related diseases associated with Down's syndrome: a record linkage study. <i>Archives of Disease in Childhood</i> 89: 1014–8</p> <p>Bonamico M, Pasquino AM, Mariani P, et al. (2002) Prevalence and clinical picture of celiac disease in Turner syndrome. <i>Journal of Clinical Endocrinology and Metabolism</i> 87: 5495–8</p> <p>Francis J, Carty JE, Scott BB (2002) The prevalence of coeliac disease in rheumatoid arthritis. <i>European Journal of Gastroenterology and Hepatology</i> 14: 1355–6</p> <p>Bonamico M, Mariani P, Danesi HM, et al. (2001) Prevalence and clinical picture of celiac disease in Italian Down syndrome patients: a multicenter study. <i>Journal of Pediatric Gastroenterology and Nutrition</i> 33: 139–43</p> <p>George EK, Hertzberger-Ten Cate R, Suijlekom-Smit LW, et al. (1996) Juvenile chronic arthritis and coeliac disease in The Netherlands. <i>Clinical and Experimental Rheumatology</i> 14: 571–5</p> <p><u>Sample of papers identified by NICE CG86 for c)</u></p> <p>Ludvigsson JF, Michaelsson K, Ekbom A, et al. (2007) Coeliac disease and the risk of fractures – a general population-based cohort study. <i>Alimentary Pharmacology and Therapeutics</i> 25: 273–85.</p> <p>Silano M, Volta U, Mecchia AM, et al. (2007) Delayed diagnosis of coeliac disease increases cancer risk. <i>BMC Gastroenterology</i> 7: 8</p> <p>Greco L, Veneziano A, Di Donato L, et al. (2004) Undiagnosed coeliac disease does not appear to be associated with unfavourable outcome of pregnancy. <i>Gut</i> 53: 149–51</p> <p>Green PHR, Fleischauer AT, Bhagat G, et al. (2003) Risk of malignancy in patients with celiac disease. <i>American Journal of Medicine</i> 115: 191–5</p>	

	Details	Additional comments
<b>Review question 4.4</b>	Should active case-finding be implemented in people with co-existing conditions/subgroups that are associated with an increased risk of coeliac disease?	Address Q2 after Q1
<b>Objectives</b>	To establish if patients with specific health conditions or specific subgroups with an increased risk of coeliac disease should be proactively investigated for coeliac disease?	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	Systematic review Prospective cohort study Population based screening studies	
<b>Status</b>	Published papers only (full text)	
<b>Population</b>	Children, young people and adults without a formal diagnosis of coeliac disease.	
<b>Intervention</b>	Active case-finding strategies (including frequency of testing)	
<b>Comparator</b>	No active case-finding	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Risk of coeliac disease</li> <li>• Risk of/event rates of complications</li> <li>• Growth in children and young people</li> <li>• Resource use and cost</li> <li>• Health-related quality of life</li> </ul>	
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>• Case studies or case series</li> <li>• Non coeliac disease gluten sensitivity</li> <li>• Wheat allergy and sensitivity</li> </ul>	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	Appropriate NICE Methodology Checklists, depending on study designs, 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-analytic approach will be used to give an overall summary effect.  All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.	
<b>Identified papers</b>	<p><u>Systematic Reviews:</u> Dretzke J, Cummins C, Sandercock J, et al. (2004) Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus. Health Technology Assessment 8(22):1-196</p> <p><u>Sample of papers identified by NICE CG86:</u> Salardi S, Volta U, Zucchini S, et al. (2008) Prevalence of celiac disease in children with type 1 diabetes mellitus increased in the mid-1990s: an 18-year longitudinal study based on anti-endomysial antibodies. Journal of Pediatric Gastroenterology and Nutrition 46: 612–4 Leeds JS, Sanders DS (2007) Is there an association between coeliac disease and irritable bowel syndrome? Gut 56: 1326–7 Guliter S, Yakaryilmaz F, Ozkurt Z, et al. (2007) Prevalence of coeliac disease in patients with autoimmune thyroiditis in a Turkish population. World Journal of Gastroenterology 13: 1599–601 Goldacre MJ, Wotton CJ, Seagroatt V, et al. (2004) Cancers and immune related diseases</p>	

	<p>associated with Down's syndrome: a record linkage study. <i>Archives of Disease in Childhood</i> 89: 1014–8</p> <p>Bonamico M, Pasquino AM, Mariani P, et al. (2002) Prevalence and clinical picture of celiac disease in Turner syndrome. <i>Journal of Clinical Endocrinology and Metabolism</i> 87: 5495–8</p> <p>Francis J, Carty JE, Scott BB (2002) The prevalence of coeliac disease in rheumatoid arthritis. <i>European Journal of Gastroenterology and Hepatology</i> 14: 1355–6</p> <p>Bonamico M, Mariani P, Danesi HM, et al. (2001) Prevalence and clinical picture of celiac disease in Italian Down syndrome patients: a multicenter study. <i>Journal of Pediatric Gastroenterology and Nutrition</i> 33: 139–43</p> <p>George EK, Hertzberger-Ten Cate R, Suijlekom-Smit LW, et al. (1996) Juvenile chronic arthritis and coeliac disease in The Netherlands. <i>Clinical and Experimental Rheumatology</i> 14: 571–5</p>
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	Details	Additional comments
<b>Review question 5.1</b>	What is the sensitivity and specificity of the serological tests for coeliac disease? Are the sensitivity and specificity results different in any specified subgroups?	
<b>Objectives</b>	To determine the accuracy of the different serological tests for coeliac disease and any subgroups of people for whom the accuracy varies.	
<b>Type of review</b>	Diagnostic test accuracy	
<b>Language</b>	English only	
<b>Study design</b>	Systematic review Test-and-treat RCT Cross-sectional study If insufficient evidence is identified, will also include: Cohort study Case-control	
<b>Status</b>	Published papers only (full text)	
<b>Population</b>	Children, young people and adults with suspected coeliac disease.	
<b>Index test</b>	Serological tests: <ul style="list-style-type: none"> <li>Immunoglobulin A tissue transglutaminase antibodies (IgA tTGA)</li> <li>Immunoglobulin A endomysial antibodies (IgA EMA)</li> <li>Immunoglobulin G tissue transglutaminase antibodies (IgG tTGA)</li> <li>Immunoglobulin G endomysial antibodies (IgG EMA)</li> <li>Human leukocyte antigen (HLA) DQ2/DQ8 testing</li> <li>Deamidated gliadin peptide (DGP) antibodies</li> </ul>	Both recombinant as well as animal tissue tTG tests will be included. Note for extracting data: different kits/platforms used for individual serological tests may have different sensitivity/specificity (for example, there are a number of different tTGA kits from different manufacturers)
<b>Reference standard</b>	Intestinal biopsy <i>(Head to head comparisons of different serological tests against intestinal biopsy)</i>	Exclude capsule biopsy
<b>Outcomes</b>	Clinical utility or diagnostic test accuracy (if available) including: <ul style="list-style-type: none"> <li>Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio, and area under the ROC analyses.</li> <li>Test validity such as face validity, content validity, construct validity, concurrent validity, criterion validity;</li> <li>Test reliability such as internal reliability/consistency, test-retest reliability, inter-rater reliability.</li> </ul> Health-related quality of life Resource use and cost	
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>Self-diagnosis kits</li> <li>Point of care testing</li> <li>Immunoglobulin G antigliadon antibody (IgG AGA)</li> <li>Immunoglobulin A antigliadon antibody</li> </ul>	

	(IgA AGA)	
<b>Search strategies</b>	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
<b>Review strategies</b>	<p>QUADAS-2 tool will be used as a guide to appraise the quality of individual studies.</p> <p>Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>If there is sufficient data, subgroup analyses may be performed on different kids/platforms for different serological tests; subgroup analysis may also be performed for recombinant and animal tissue tTG tests.</p> <p>All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p> <p>Sub-analysis will be undertaken by subgroups of patients where appropriate</p>	



<b>Identified papers</b>	<p><u>Systematic Reviews:</u></p> <p>Ford A C , Chey W D , Talley N J et al. (2009) Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome (Structured abstract). Archives of Internal Medicine 169(7), 651-658</p> <p>Giersiepen K , Lelgemann M , Stuhldreher N et al. (2012) Accuracy of diagnostic antibody tests for coeliac disease in children: summary of an evidence report (Provisional abstract). Journal of Pediatric Gastroenterology and Nutrition 54(2):229-241</p> <p>Lewis NR, Scott BB. (2010) Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Alimentary Pharmacology and Therapeutics 31(1):73-81</p> <p>Van der Windt DA, Jellema P, Mulder CJ, et al. (2010) Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. JAMA 303(17):1738-1746</p> <p>Medical Advisory Secretariat, Ontario Ministry of Health and Long- Term Care (MAS) (2010) Clinical utility of serologic testing for celiac disease in Ontario (symptomatic patients).</p> <p>Pichon-Riviere,A.; Augustovski,F.; Galante,J. (2009) Detection of deamidated gliadin peptides for the diagnosis of celiac disease. Ciudad de Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS)</p>
	<p><u>Sample of papers identified in NICE CG86:</u></p> <p>Emami MH (2008) Diagnostic accuracy of IgA anti-tissue transglutaminase in patients suspected of having coeliac disease in Iran. Journal of Gastrointestinal and Liver Diseases 17: 141–6</p> <p>Agardh D (2007) Antibodies against synthetic deamidated gliadin peptides and tissue transglutaminase for the identification of childhood celiac disease. Clinical Gastroenterology and Hepatology 5: 1276–81</p> <p>Abrams JA, Brar P, Diamond B, et al. (2006) Utility in clinical practice of immunoglobulin A anti-tissue transglutaminase antibody for the diagnosis of celiac disease. Clinical Gastroenterology and Hepatology 4: 726–30</p> <p>Bizzaro N, Tampoia M, Villalta D, et al. (2006) Low specificity of anti-tissue transglutaminase antibodies in patients with primary biliary cirrhosis. Journal of Clinical Laboratory Analysis 20: 184–9</p> <p>Reeves GE, Squance ML, Duggan AE, et al. (2006) Diagnostic accuracy of coeliac serological tests: a prospective study. European Journal of Gastroenterology and Hepatology 18: 493–501</p> <p>Johnston SD, McMillan SA, Collins JS, et al. (2003) A comparison of antibodies to tissue transglutaminase with conventional serological tests in the diagnosis of coeliac disease. European Journal of Gastroenterology and Hepatology 15: 1001–4</p>

	Details	Additional comments
<b>Review question 5.2</b>	<p>Which serological test is the most appropriate to diagnose coeliac disease?</p> <p>Depending on test results, should more than one test be used and, if so, what should be the sequence of testing?</p> <p>Following which sequence of tests and test results is it appropriate to refer onwards for endoscopic intestinal biopsy for confirmatory diagnosis?</p>	
<b>Objectives</b>	<p>To determine when:</p> <ol style="list-style-type: none"> <li>serological test results indicate a diagnosis of coeliac disease without need for intestinal biopsy</li> <li>serological test results indicate a referral for intestinal biopsy for confirmatory diagnosis is appropriate.</li> </ol>	
<b>Type of review</b>	Diagnostic (Diagnostic strategy/pathway)	Diagnostic strategy/pathway that involves parallel or sequential/serial testing
<b>Language</b>	English only	
<b>Study design</b>	<p>Systematic review</p> <p>Test-and-treat RCT</p> <p>Cross-sectional study</p> <p>If insufficient evidence is identified, will also include:</p> <p>Cohort study</p> <p>Case-control</p>	
<b>Status</b>	Published papers only (full text)	
<b>Population</b>	Children, young people and adults with suspected coeliac disease.	
<b>Index test</b>	<p>Combinations (parallel or sequential) of serological and IgA deficiency testing</p> <p>Various criteria for referral to a gastrointestinal specialist for intestinal biopsy for confirmatory diagnosis following serological and IgA deficiency testing</p>	
<b>Reference standard(s)</b>	<p>Intestinal biopsy</p> <p>Standard serological and IgA deficiency test algorithms, including test algorithm in NICE CG86.</p>	<p>Exclude capsule biopsy.</p> <p>Testing algorithm in NICE CG86:</p> <ul style="list-style-type: none"> <li>IgA tTGA as first line test</li> <li>IgA EMA if above is equivocal</li> <li>IgA deficiency testing if either above are negative</li> <li>IgG tTGA and/or IgG EMA if confirmed IgA deficiency</li> <li>Referral if any tTGA or EMA test above is positive.</li> </ul>
<b>Outcomes</b>	<p>Clinical utility or diagnostic test accuracy (if available) including:</p> <ul style="list-style-type: none"> <li>Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio and area under the ROC analyses.</li> <li>Test validity such as face validity, content validity, construct validity, concurrent validity, criterion validity;</li> <li>Test reliability such as internal reliability/consistency, test-retest reliability, inter-rater reliability.</li> </ul> <p>Health-related quality of life</p>	

	Resource use and cost	
<b>Other criteria for inclusion / exclusion of studies</b>	<p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Self-diagnosis kits</li> <li>• Point of care testing</li> <li>• Immunoglobulin G anti gliadon antibody (IgG AGA)</li> <li>• Immunoglobulin A anti gliadon antibody (IgA AGA)</li> </ul>	
<b>Search strategies</b>	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
<b>Review strategies</b>	<p>QUADAS-2 tool will be used as a guide to appraise the quality of individual studies.</p> <p>Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p> <p>Sub-analysis will be undertaken by subgroups of patients where appropriate</p>	
<b>Identified papers</b>	<p><u>Systematic Reviews:</u></p> <p>Lewis N R, Scott B B, (2006) Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests) <i>Alimentary Pharmacology and Therapeutics</i>.2006;24(1):47-54</p> <p>Ford A C , Chey W D , Talley N J et al. (2009) Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome (Structured abstract). <i>Archives of Internal Medicine</i> 169(7), 651-658</p> <p>Lewis NR, Scott BB. (2010) Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. <i>Alimentary Pharmacology and Therapeutics</i> 31(1):73-81</p> <p>van der Windt DA, Jellema P, Mulder CJ, et al. (2010) Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. <i>JAMA</i> 303(17):1738-1746</p> <p><u>Sample of papers identified in NICE CG86:</u></p> <p>Hopper AD, Hadjivassiliou M, Hurlstone DP, et al. (2008) What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. <i>Clinical Gastroenterology and Hepatology</i> 6: 314–20</p>	

	Details	Additional comments
<b>Review question 5.3</b>	What are the referral indications for endoscopic intestinal biopsy for further investigation in people with coeliac disease?	
<b>Objectives</b>	To establish what factors (other than the sequence of serological testing [question 4]) may indicate appropriate referral for endoscopic intestinal biopsy for people with coeliac disease.	
<b>Type of review</b>	Prognostic	
<b>Language</b>	English only	
<b>Study design</b>	No restriction (except qualitative studies and case reports)	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with diagnosed coeliac disease	This includes people with a diagnosis of coeliac disease who are being monitored and in whom an intestinal biopsy may be useful in further investigation to monitor treatment.
<b>Prognostic factor</b>	Indications (other than the sequence of serological testing [question 4]) may indicate appropriate referral for endoscopic intestinal biopsy	
<b>Comparator</b>	Not applicable	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Complications of coeliac disease</li> <li>• Mortality</li> <li>• Health related quality of life</li> <li>• Resource use and cost</li> </ul>	Complications include, but are not limited to: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• ulcerative jejunitis</li> <li>• malignancy (intestinal lymphoma)</li> <li>• functional hyposplenism</li> <li>• vitamin D deficiency</li> <li>• iron deficiency</li> <li>• auto-immune diseases</li> </ul>
<b>Other criteria for inclusion / exclusion of studies</b>	<p>Exclusion :</p> <ul style="list-style-type: none"> <li>• Non coeliac disease gluten sensitivity</li> <li>• Studies examining clinical utility of serological testing</li> <li>• Wheat allergy and sensitivity</li> <li>• Use of intestinal biopsy for initial diagnosis</li> <li>• Aspects related to routine monitoring (this is covered in question 7)</li> </ul>	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	<p>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p>	
<b>Identified papers</b>	None.	

	Details	Additional comments
<b>Review question 5.4</b>	a) How frequently should people with coeliac disease be routinely monitored? b) Should the frequency of routine monitoring differ for patients with at risk of developing certain complications? c) What should routine monitoring consist of?	
<b>Objectives</b>	a) To determine how often people with coeliac disease should be followed up b) To determine if any subgroups at risk of developing any particular complications should be followed up more frequently c) To determine what assessments and checks should be carried out to monitor coeliac disease, particularly those at risk of developing complications.	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	Systematic review RCTs If insufficient evidence is identified, will also include: Non-randomised controlled trials Prospective cohort study	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with coeliac disease	
<b>Intervention</b>	a) Different follow-up frequencies b) Different follow-up frequencies c) Monitoring strategies, tests and techniques.	Monitoring strategies could include bone density assessment, serology, histology, dietary assessment (adherence and quality of diet), symptomatic response
<b>Comparator</b>	a) Standard care or comparing different frequencies of follow-up b) Standard care or comparing different frequencies of follow-up c) Standard care (without specific monitoring strategies)	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Resolution of gastrointestinal and non-gastrointestinal symptoms</li> <li>• Growth in children and young people</li> <li>• Complications of coeliac disease</li> <li>• Dietary adherence</li> <li>• Impact on carers</li> <li>• Health-related quality of life</li> <li>•</li> </ul>	Complications include: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• ulcerative jejunitis</li> <li>• malignancy (intestinal lymphoma)</li> <li>• functional hyposplenism</li> <li>• vitamin D deficiency</li> <li>• iron deficiency</li> <li>• auto-immune diseases</li> </ul>
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>• Case series and case studies</li> <li>• Non coeliac disease gluten sensitivity</li> <li>• Wheat allergy or sensitivity</li> </ul>	
<b>Search strategies</b>	.....	
<b>Review</b>	Appropriate NICE Methodology Checklists,	

<b>strategies</b>	<p>depending on study designs, will be used as a guide to appraise the quality of individual studies.</p> <p>Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.</p> <p>Sub-analysis will be undertaken for people at risk of developing complications; adults vs. children, if appropriate.</p>	
<b>Identified papers</b>	<p><u>For a):</u> <u>Studies</u> Liu, Brais, Lavergene-Slove et al (2012) Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease. Gut, 04 2010, vol./is. 59/4(452-60), 0017-5749;1468-3288 Malamut, Afchain,</p> <p><u>For b):</u> <u>Studies</u> Hutchinson, West, Robins and Howdle (2010) Long-term histological follow-up of people with coeliac disease in a UK teaching hospital. Qjm, 07 2010, vol./is. 103/7(511-7), 1460-2393;1460-2393 Vecsei, Graf and Vogelsang (2009) Follow-up of adult celiac patients: which non-invasive test reflects mucosal status most reliability. Endoscopy, 02 2009, vol./is. 41/2(123-8), 0013-726X;1438-8812 Bonamico, Nenna, Luparia et al ( 2008) Radioimmunological detection of anti-transglutaminase autoantibodies in human saliva: a useful test to monitor coeliac disease follow-up. Alimentary Pharmacology &amp; Therapeutics, 08 2008, vol./is. 28/3(364-70), 0269-2813;0269-2813</p>	

	Details	Additional comments
<b>Review question 6.1</b>	a) What are the potential causes of non-responsive coeliac disease?	<p>This question will identify the proportion of patients with non-responsive disease who fall into each of the following categories:</p> <p>Continued ingestion of gluten</p> <ul style="list-style-type: none"> <li>• Poor compliance</li> <li>• Inadvertent (contamination)</li> </ul> <p>Co-existing conditions:</p> <ul style="list-style-type: none"> <li>• Lactose or fructose intolerance</li> <li>• Other food intolerances</li> <li>• Pancreatic insufficiency</li> <li>• Microscopic colitis</li> <li>• Bacterial overgrowth</li> <li>• Collagenous colitis or collagenous sprue</li> <li>• Irritable bowel syndrome</li> <li>• Ulcerative jejunitis</li> <li>• Enteropathy (including autoimmune enteropathy)</li> <li>• associated T-cell lymphoma</li> <li>• Functional disorders</li> <li>• Common variable immunodeficiency</li> </ul> <p>Refractory coeliac disease</p>
<b>Objectives</b>	To determine the proportion of differing causes of persistent symptoms in patients with a confirmed diagnosis of coeliac disease who have been advised to exclude gluten from the diet	
<b>Type of review</b>	Prevalence	
<b>Language</b>	English only	
<b>Study design</b>	Systematic review Case series Cross-sectional study	
<b>Status</b>	Published (full text only)	
<b>Population</b>	All children, young people and adults with a biopsy confirmed diagnosis of coeliac disease, who have been advised by a health professional to exclude gluten from the diet and who have had persistent symptoms for more than 6 months.	Under 18s and 18 and over will be assessed separately. Other age sub-groups will be included if this appears to be relevant from the studies found
<b>Index test(s)</b>	Not relevant	
<b>Reference standard(s)</b>	Not relevant	
<b>Outcomes</b>	Proportion of differing causes of non-responsiveness, which should be considered as part of the differential diagnosis of non-responsive coeliac disease	
<b>Other criteria for inclusion / exclusion of studies</b>	<p>Exclusion:</p> <p>Non biopsy confirmed</p> <p>Symptoms persisting less than 6 months</p> <p>No health care professional advice on gluten free</p>	Depending on the studies found it may be relevant to further analyse the data after excluding the proportion of patients with continued gluten ingestion (as the latter proportion may be influenced by the level of dietary advice and support and food labelling in different countries)

	diet	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	<p>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.</p> <p>Data on all included studies will be extracted into evidence tables. Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p>	
<b>Identified papers</b>	<p><u>Studies</u></p> <p>O'Shea, Abuzakouk, O'Morain et al (2008) Investigation of molecular markers in the diagnosis of refractory coeliac disease in a large patient cohort. <i>Journal of Clinical Pathology</i>, 11 2008, vol./is. 61/11(1200-2), 0021-9746;1472-4146</p> <p>Barret, Malamut, Rahmi et al (2012) Diagnostic yield of capsule endoscopy in refractory celiac disease. <i>American Journal of Gastroenterology</i>, 10 2012, vol./is. 107/10(1546-53), 0002-9270;1572-0241</p> <p>Van Weyenberg, Meijerink, Jacobs et al (2011) MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system. <i>Radiology</i>, 04 2011, vol./is. 259/1(151-61), 0033-8419;1527-1315</p>	



	Details	Additional comments
<b>Review question 6.1</b>	<p>b) In patients with confirmed refractory coeliac disease what investigative procedures should be undertaken, such as:</p> <ul style="list-style-type: none"> <li>• Clonality assessment</li> <li>• Flow cytometry</li> <li>• Aberrant T cell assessment</li> <li>• Immunophenotyping</li> <li>• Imaging</li> </ul>	<p>This question will inform how to investigate patients with suspected refractory coeliac disease</p> <p>Tests that will guide the ongoing clinical management, such as assessing the risk of lymphoma</p>
<b>Objectives</b>	To determine the proportion of differing causes of persistent symptoms in patients with a confirmed diagnosis of coeliac disease who have been advised to exclude gluten from the diet	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	<p>Systematic review  Test-and-Treat RCT  Cross-sectional study  If insufficient evidence is identified, will also include:  Cohort study  Case-control</p>	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Patients with a confirmed diagnosis of coeliac disease, <i>in whom persistent villous atrophy is found on biopsy</i> , and in whom continued exposure to gluten and co-existing conditions (causing the symptoms) have been excluded	Under 18s and 18 and over will be assessed separately. Other age sub-groups will be included if this appears to be relevant from the studies found
<b>Intervention</b>	<p>Investigative tests:</p> <ul style="list-style-type: none"> <li>• Clonality assessment</li> <li>• Flow cytometry</li> <li>• Aberrant T cell assessment</li> <li>• Immunophenotyping</li> <li>• Imaging</li> </ul>	
<b>Comparator</b>	Do nothing	
<b>Outcomes</b>	<p>Clinical utility:</p> <ul style="list-style-type: none"> <li>• Change to clinical management</li> <li>• Resource use and cost</li> <li>• Patient outcomes at follow up</li> <li>• Health-related quality of life</li> </ul>	
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: None	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	<p>Appropriate NICE Methodology Checklists, depending on study designs, 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</p>	

	<p>meta-analytic approach will be used to give an overall summary effect.</p> <p>All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p>	
<p><b>Identified papers</b></p>	<p><u>Studies</u></p> <p>O’Shea, Abuzakouk, O’Morain et al (2008) Investigation of molecular markers in the diagnosis of refractory coeliac disease in a large patient cohort. <i>Journal of Clinical Pathology</i>, 11 2008, vol./is. 61/11(1200-2), 0021-9746;1472-4146</p> <p>Barret, Malamut, Rahmi et al (2012) Diagnostic yield of capsule endoscopy in refractory celiac disease. <i>American Journal of Gastroenterology</i>, 10 2012, vol./is. 107/10(1546-53), 0002-9270;1572-0241</p> <p>Van Weyenberg, Meijerink, Jacobs et al (2011) MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system. <i>Radiology</i>, 04 2011, vol./is. 259/1(151-61), 0033-8419;1527-1315</p>	

	Details	Additional comments
<b>Review question 6.2</b>	What is the effectiveness of pharmacological treatments for people with refractory coeliac disease?	
<b>Objectives</b>	To determine what medication can help treat coeliac disease that is not responding to dietary management and when other diagnoses have been excluded.	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	Systematic review RCTs Case series	Originally the GDG were interested in only considering studies with a control group but as no studies were found, they chose to include case series as well
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with refractory coeliac disease	
<b>Intervention</b>	Pharmacological treatments for refractory coeliac disease which include, but are not limited to: <ul style="list-style-type: none"> <li>• Anti-TNF (including infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira], golimumab [Simponi], certolizumab [Cimzia])</li> <li>• ASA preparation/Mesalazine/Mesalamine (Apriso, Asacol, Canasa, Lialda, pentasa, Rowasa)</li> <li>• Azathioprine (Imuran)</li> <li>• Prednisolone (Ak-Pred, Articulose-50, AsmalPred Plus, Delta-Cortef, Econopred, etc)</li> <li>• Budesonide (Entocort, Pulmicort, Rhinocort, Symbicort)</li> <li>• Cladribine (Leustatin)</li> <li>• Cyclosporin (Gengraf, Neoral, Restasis, Sandimmune)</li> <li>• Thioguanine (Tabloid)</li> <li>• Other corticosteroids (other than prednisolone and budesonide)</li> </ul>	
<b>Comparator</b>	Standard care (including gluten-free diet) Placebo Head to head comparison	It is important to note which gluten free diet patients were on (eg gluten & wheat free). Check country and year of paper. Elemental diets have been used.
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Resolution of gastrointestinal and non-gastrointestinal symptoms</li> <li>• Complications of coeliac disease</li> <li>• Adverse effects</li> <li>• Health-related quality of life</li> <li>• Impact on carers</li> <li>• Serological response</li> <li>• Histological response</li> <li>•</li> </ul>	Complications include, but are not limited to: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• ulcerative jejunitis</li> <li>• malignancy (intestinal lymphoma)</li> <li>• functional hyposplenism</li> <li>• vitamin D deficiency</li> <li>• iron deficiency</li> <li>• auto-immune diseases</li> </ul>
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>• Case reports</li> </ul>	

<b>Search strategies</b>	.....	
<b>Review strategies</b>	<p>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.</p>	
<b>Identified papers</b>	<p>Studies</p> <p>Tack, Verbeek, Al-Toma et al (2011) Evaluation of Cladribine treatment in refractory celiac disease type II. <i>World Journal of Gastroenterology</i> 17(4): 506–513.</p> <p>Jamma, Leffler, Dennis et al (2011) Small intestinal release mesalamine for the treatment of refractory celiac disease type I. <i>Journal of Clinical Gastroenterology</i>, 01 2011, vol./is. 45/1(30-3), 0192-0790;1539-2031</p> <p>Brar, Lee, Lewis et al (2007) Budenoside in the treatment of refractory celiac disease. <i>American Journal of Gastroenterology</i>, 10 2007, vol./is. 102/10(2265-9), 0002-9270;0002-9270</p> <p>Al-Toma, Verbeek, Hadithi et al (2007) Survival in refractory coeliac disease and enteropathy –associated T-cell lymphoma: retrospective evaluation of single-centre experience. <i>Gut</i>, 10 2007, vol./is. 56/10(1373-8), 0017-5749;0017-5749</p> <p>Goerres, Meijer, Wahab et al (2003) Azathioprine and prednisone combination therapy in refractory coeliac disease. <i>Alimentary Pharmacology &amp; Therapeutics</i>, 09 2003, vol./is. 18/5(487-94), 0269-2813;0269-2813</p>	

	Details	Additional comments
<b>Review question 6.3</b>	What is the effectiveness of nutritional management or nutritional support for people with refractory coeliac disease?	
<b>Objectives</b>	To determine what additional nutritional support (beyond advice on changes to the diet) can help treat coeliac disease that is not responding to dietary management and when other diagnoses have been excluded.	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	Systematic review RCTs If insufficient evidence is identified, will also include: Non-randomised controlled trials Prospective cohort study	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with refractory coeliac disease	
<b>Intervention</b>	Nutritional support for people with refractory coeliac disease which includes, but is not limited to: <ul style="list-style-type: none"> <li>• Further dietary exclusions</li> <li>• Oral nutrition support (for example, fortified food)</li> <li>• Enteral tube feeding (delivery of nutrition into the gut)</li> <li>• Parenteral nutrition (delivery of nutrition intravenously)</li> </ul>	Further dietary exclusions could include high allergenic foods such as soya, milk, egg, etc
<b>Comparator</b>	Standard care Placebo Head to head comparison	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Resolution of gastrointestinal and non-gastrointestinal symptoms</li> <li>• Complications of coeliac disease</li> <li>• Adverse events</li> <li>• Health-related quality of life</li> <li>• Impact on carers</li> <li>• Serological response</li> </ul>	Complications include, but are not limited to: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• ulcerative jejunitis</li> <li>• malignancy (intestinal lymphoma)</li> <li>• functional hyposplenism</li> <li>• vitamin D deficiency</li> <li>• iron deficiency</li> <li>• auto-immune diseases</li> </ul>
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>• Retrospective cohort study, case series and case reports.</li> </ul>	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	Appropriate NICE Methodology Checklists, depending on study designs, 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-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be	

	presented in GRADE profiles and further summarised in evidence statements.	
<b>Identified papers</b>	<p>Studies</p> <p>Jamma, Rubio-Tapia, Kelly et al (2010) Celiac crisis is a rare but serious complication of celiac disease in adults. <i>Clinical Gastroenterology &amp; Hepatology</i>, 07 2010, vol./is. 8/7(587-90), 1542-3565;1542-7714</p>	

	Details	Additional comments
<b>Review question 6.4</b>	What is the effectiveness of autologous stem cell transplant for people with refractory coeliac disease?	
<b>Objectives</b>	To determine how effective it is to treat refractory coeliac disease with chemotherapy followed by transplantation of stem cells from the patient's own body.	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	No restriction except qualitative studies and case reports.	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with refractory coeliac disease	
<b>Intervention</b>	Chemotherapy followed by autologous stem cell transplant	
<b>Comparator</b>	Standard care Placebo Head to head comparison with pharmacological treatments	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Health-related quality of life</li> <li>• Impact on carers</li> <li>• Resolution of gastrointestinal and non-gastrointestinal symptoms</li> <li>• Complications of coeliac disease</li> <li>• Complications from surgery</li> <li>• Serological response</li> <li>• Adverse events</li> </ul>	Complications include, but are not limited to: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• ulcerative jejunitis</li> <li>• malignancy (intestinal lymphoma)</li> <li>• functional hyposplenism</li> <li>• vitamin D deficiency</li> <li>• iron deficiency</li> <li>• auto-immune diseases</li> </ul>
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>• Qualitative studies and case reports</li> </ul>	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	Appropriate NICE Methodology Checklists, depending on study designs, 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-analytic approach will be used to give an overall summary effect. All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.	
<b>Identified papers</b>	None identified	

	Details	Additional comments
<b>Review question 7.1</b>	<p>What information do people (and their family members or carers, as appropriate) need to help them decide whether to undergo initial testing for coeliac disease?</p> <p>If people are to undergo initial testing, what dietary information do they (or their family members or carers) need before testing to ensure that test results are as accurate as possible?</p>	
<b>Objectives</b>	<p>To establish what information is needed by patients to:</p> <ul style="list-style-type: none"> <li>• help decide whether to be tested for coeliac disease</li> <li>• manage their diet before being tested</li> </ul>	
<b>Type of review</b>	Information and support	
<b>Language</b>	English only	
<b>Study design</b>	No restriction except case reports	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults being investigated for coeliac disease	
<b>Intervention</b>	<p>Information strategies to help people decide whether to be tested for coeliac disease</p> <p>Information to help people to manage their diet prior to the tests (to improve the accuracy of the tests).</p>	Information needs may be different (and include more specific information) for patients at higher risk and some of these patients may be asymptomatic
<b>Comparator</b>	N/A	
<b>Outcomes</b>	<p>Any information identified</p> <p>Patient experience</p> <p>Resource use and cost</p>	
<b>Other criteria for inclusion / exclusion of studies</b>	Case reports	
<b>Search strategies</b>	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
<b>Review strategies</b>	<p>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p> <p>Separate analysis will be performed where appropriate for parents and carers.</p>	
<b>Identified papers</b>	None.	



	Details	Additional comments
<b>Review question 7.2</b>	<p>a) What information, education and support do people with coeliac disease (and their family members or carers, as appropriate) need to improve adherence to a gluten-free diet and self-management of their condition?</p> <p>b) What is the patient perspective of self-management and how to improve adherence, including what information is required, different monitoring strategies, and with whom they are followed up?</p>	
<b>Objectives</b>	<p>To establish what information, education and support is needed by people with coeliac disease to help them follow a gluten-free diet and manage their own condition.</p> <p>To elicit preferences of patients to improve their self-management including information, different monitoring strategies, and with who they are followed up.</p>	
<b>Type of review</b>	<p>a) Intervention (for effectiveness of any educational or support programmes/strategies to improve adherence)</p> <p>b) Qualitative (patient experiences about required information and monitoring strategies to improve self-management including adherence)</p>	
<b>Language</b>	English only	
<b>Study design</b>	<p>a)</p> <p>Systematic review</p> <p>RCTs</p> <p>Prospective cohort studies</p> <p>b)</p> <p>No restriction except case reports</p>	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with coeliac disease	
<b>Intervention</b>	<p>a)</p> <p>Any educational or support programmes/strategies to improve adherence</p> <p>b)</p> <p>Any information needs identified</p>	
<b>Comparator</b>	<p>a) Standard care</p> <p>b) N/A</p>	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Resolution of gastrointestinal and non-gastrointestinal symptoms</li> <li>• Patient experience</li> <li>• Complications of coeliac disease</li> <li>• Resource use and cost</li> <li>• Adherence</li> <li>• Health-related quality of life</li> <li>• Impact on carers</li> <li>•</li> </ul>	
<b>Other criteria for inclusion / exclusion of studies</b>	<p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Non coeliac disease gluten sensitivity</li> <li>• Wheat allergy and sensitivity</li> </ul>	

<b>Search strategies</b>	.....	
<b>Review strategies</b>	<p>Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.</p> <p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All prioritised key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.</p> <p>Separate analysis will be performed where possible for parents and carers.</p>	
<b>Identified papers</b>	None.	

	Details	Additional comments
<b>Review question 7.3</b>	a) What dietary management strategy/advice should be given to people with coeliac disease? b) Should the advice include avoiding gluten-free oats as part of the exclusion diet?	
<b>Objectives</b>	To determine what other dietary management strategy/advice should be given to people with coeliac disease.	
<b>Type of review</b>	Intervention	
<b>Language</b>	English only	
<b>Study design</b>	Systematic reviews RCTs If insufficient evidence is identified, will also include: Non-randomised controlled trials Prospective cohort studies	
<b>Status</b>	Published (full text only)	
<b>Population</b>	Children, young people and adults with coeliac disease	
<b>Intervention</b>	a) Any dietary management/advice other than a gluten-free diet The use of nutritional supplements as 'other dietary advice' will only include: <ul style="list-style-type: none"> <li>• calcium</li> <li>• Vitamin D</li> <li>• Vitamin B12</li> <li>• Iron</li> <li>• Folic acid</li> </ul> b) Use of gluten-free oats as part of the exclusion diet (including thresholds for oats intake)	
<b>Comparator</b>	Gluten free diet only (standard care)	
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Resolution of gastrointestinal and non-gastrointestinal symptoms</li> <li>• Growth in children and young people</li> <li>• Complications of coeliac disease</li> <li>• Dietary adherence</li> <li>• Impact on carers</li> <li>• Health-related quality of life</li> <li>• Serological response</li> <li>• Histological response</li> </ul>	Complications include, but are not limited to: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• ulcerative jejunitis</li> <li>• malignancy (intestinal lymphoma)</li> <li>• functional hyposplenism</li> <li>• vitamin D deficiency</li> <li>• iron deficiency</li> <li>• auto-immune diseases</li> </ul>
<b>Other criteria for inclusion / exclusion of studies</b>	Exclusion: <ul style="list-style-type: none"> <li>• Case series and case studies</li> <li>• Non coeliac disease gluten sensitivity</li> <li>• Wheat allergy and sensitivity</li> </ul>	
<b>Search strategies</b>	.....	
<b>Review strategies</b>	Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies. Data on all included studies will be extracted into evidence tables.	

	<p>Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.</p> <p>All prioritised key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.</p>	
<b>Identified papers</b>	<p><u>Systematic Reviews:</u></p> <p>Pulido OM, Gillespie Z, Zarkadas M, et al. (2009) Introduction of oats in the diet of individuals with celiac disease: a systematic review. <i>Advances in Food and Nutrition Research</i> 57(6):235-285</p> <p>Haboubi, Taylor and Jones (2006) Coeliac disease and oats: a systematic review. <i>Postgraduate Medical Journal</i>.2006;82(972):672-678</p> <p><u>Studies</u></p> <p>Villaneuva, Maranda and Nwosu (2012) Is vitamin D deficiency a feature of pediatric celiac disease? <i>Journal of Pediatric Endocrinology</i>, 2012, vol./is. 25/5-6(607-10), 0334-018X;0334-018X (2012)</p> <p>Hadithi, Mulder, Stam et al (2009) Effect of B vitamin supplementation on plasma homocysteine levels in celiac disease. <i>World Journal of Gastroenterology</i>, 02 2009, vol./is. 15/8(955-60), 1007-9327;1007-9327</p> <p>Mager, Qiao and Turner (2012) Vitamin D and K status influences bone mineral density and bone accrual in children and adolescents with celiac disease. <i>European Journal of Clinical Nutrition</i>, 04 2012, vol./is. 66/4(488-95), 0954-3007;1476-5640</p> <p>Hallert, Grant, Grehn et al (2002) Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. <i>Alimentary Pharmacology &amp; Therapeutics</i>, 07 2002, vol./is. 16/7(1333-9), 0269-2813;0269-2813.</p>	