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
• Audit Commission • British Dietetic Association • British Nutrition Foundation • British Society of Gastroenterology • British Society of Paediatric Gastroenterology, Hepatology and Nutrition • Care Quality Commission • Coeliac UK • COMET • Department of Health • Guidelines International Network (GIN) • Healthcare Improvement Scotland • Health Protection Agency • King´s Fund • National Audit Office • National Patient Safety Agency • National Institute for Health and Clinical Excellence (NICE) - published & in development guidelines • National Institute for Health and Clinical Excellence (NICE) - Topic Selection • National Institute for Innovation and Improvement • National Patient Safety Agency • National Prescribing Centre • NHS Business Services Authority • NHS Evidence • NHS Information Centre • NHS Scotland • NHS Wales • New Zealand Guidelines Group • Primary Care Society for Gastroenterology • Prodigy (formerly Clinical Knowledge Summaries) • Royal Colleges • Royal Pharmaceutical Society of Great Britain • Royal Society of Medicine •	• BMJ Clinical Evidence • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • DUETS • Health Economic Evaluations Database (HEED) • Health Technology Assessment (HTA) Database • NHS Economic Evaluation Database (NHS EED) • NIHR Health Technology Assessment • NIHR Health Services and Delivery Research (HS&DR) Programme • PROSPERO • TRIP Database

• 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 wive* 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 miscarr*).tw.
154 Growth Disorders/
155 Failure to thrive/
156 (fail* adj4 thriv*).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 dysthmia 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

<Insert Note here>

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

<Insert Note here>

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

<Insert Note here>

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:**	
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	(esophagogastroduodenscop* or oesophagogastroduodenscop*).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

<Insert Note here>

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

<Insert Note here>

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	((gluterin 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	Adrenocorticotropic 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 intraintestinal 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 ((hematopoiet* or hemoatopoet* or haematopoiet* or haemoatopoet* or autolog* or allogen*) 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 ((hematopoiet* or hematopoet* or haematopoiet* 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

Medline Strategy, searched 15th November 2013 **Database: Ovid MEDLINE(R) <1946 to November Week 1 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	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 • Signs and symptoms • Populations with increased risk of coeliac disease • Long term consequences of undiagnosed coeliac disease 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
Review question 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?	
Objectives	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	
Type of review	Diagnostic (4.1) epidemiological (4.2), and prognostic (4.3)	
Language	English only	
Study design	No restriction (except qualitative studies and case reports) Case series are excluded for all but c.	
Status	Published papers only (full text)	
Population	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. **Exclusions:** • 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 • Signs and symptoms of patients after diagnosis of coeliac disease unless untreated (since treatment is likely to alter signs and symptoms) • Rates of comorbidities that develop in patients after they have been diagnosed with coeliac disease • 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)	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. 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. 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. 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. 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.

Factors/ Variables/ Predictors	4.1. Presenting clinical features: • abnormal liver enzymes • amenorrhoea • chronic or intermittent diarrhoea/constipation • dental complications (enamel deterioration) • failure to thrive, faltering growth (in children) or delayed puberty • functional hyposplenism • gluten sensitive neuropathy • intra-cerebral calcification • intussusception (bowel telescopes within self) • malignancy including intestinal lymphoma, oesophageal cancer, colonic cancer • peripheral neuropathy • persistent or unexplained gastrointestinal symptoms including nausea and vomiting • pregnancy outcomes (sub-fertility, early miscarriage, intra-uterine growth retardation, premature babies) • prolonged fatigue • sudden or unexpected weight loss, height loss or fragility fractures • ulcerative jejunitis • unexplained iron-deficiency anaemia, or other unspecified anaemia • recurrent abdominal pain, cramping or distension • recurrent aphthous-ulceration • refractory coeliac disease • reduced bone mineral density • vitamin D, vitamin B12, folic acid and iron deficiency 4.2. Coexisting conditions: • Addisons disease • all autoimmune diseases (such as autoimmune thyroid disease, autoimmune myocarditis, autoimmune hepatitis) • alopecia areata • bipolar disorder or depression • bone mineral disease (such as rickets or osteomalacia) • cardiomyopathy • chronic thrombocytopenia purpura • dermatitis herpetiformis • Downs syndrome • epilepsy • HIV • IgA deficiency	

	• irritable bowel syndrome • juvenile idiopathic arthritis • microscopic colitis • neurological conditions (ataxia, headache, peripheral neuropathy) • osteoporosis (including fracture risk) • primary biliary cirrhosis • rheumatoid arthritis • sarcoidosis • Sjogren's syndrome • Turner syndrome • type 1 diabetes • Williams syndrome Other factors /specific subgroups: • first-degree relatives with coeliac disease • lower socioeconomic status • North African communities (specifically Berber communities)	
Comparator	4.1 Confirmed diagnosis by intestinal biopsy only 4.2, 4.3 NA	
Outcome measures	Specific for 4.1) • Accuracy metrics (sensitivity, specificity, +LR, -LR, PPV, NPV, etc.) • Predictive measures from adjusted regression model Specific for 4.2) • Risk of having coeliac disease • Risk of/event rates of complications • Growth in children and young people Specific for 4.3) • Complications of coeliac disease of • Complications from the long-term consequences • Growth in children and young people Overall: • Mortality • Resource use and cost • Health related quality of life	
Other criteria for inclusion / exclusion of studies	Exclusion: • Case reports, case series (except for c), or qualitative studies • For long-term, consequences (c), studies with less than 50 patients • Non coeliac disease gluten sensitivity • Wheat allergy and sensitivity	
Search strategies	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
Review strategies	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.	
Identified papers	Sample of papers identified in NICE CG86 for a): Bottaro G, Cataldo F, Rotolo N, et al. (1999) The clinical pattern of subclinical/silent celiac disease: an analysis on 1026 consecutive cases. American Journal of Gastroenterology 94: 691–6 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 Garampazzi A, Rapa A, Mura S, et al. (2007) Clinical pattern of celiac disease is still changing. Journal of Pediatric Gastroenterology and Nutrition 45: 611–4 Vilppula A, Collin P, Maki M, et al. (2008) Undetected coeliac disease in the elderly: a biopsy-proven population-based study. Digestive and Liver Disease 40: 809–13 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? Minerva Gastroenterologica e Dietologica 48: 121–30 Systematic Reviews for b): 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 Sample of papers identified by NICE CG86 for b): 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 associated with Down's syndrome: a record linkage study. Archives of Disease in Childhood 89: 1014–8 Bonamico M, Pasquino AM, Mariani P, et al. (2002) Prevalence and clinical picture of celiac disease in Turner syndrome. Journal of Clinical Endocrinology and Metabolism 87: 5495–8 Francis J, Carty JE, Scott BB (2002) The prevalence of coeliac disease in rheumatoid arthritis. European Journal of Gastroenterology and Hepatology 14: 1355–6 Bonamico M, Mariani P, Danesi HM, et al. (2001) Prevalence and clinical picture of celiac disease in Italian Down syndrome patients: a multicenter study. Journal of Pediatric Gastroenterology and Nutrition 33: 139–43 George EK, Hertzberger-Ten Cate R, Suijlekom-Smit LW, et al. (1996) Juvenile chronic arthritis and coeliac disease in The Netherlands. Clinical and Experimental Rheumatology 14: 571–5 Sample of papers identified by NICE CG86 for c) Ludvigsson JF, Michaelsson K, Ekbom A, et al. (2007) Coeliac disease and the risk of fractures – a general population-based cohort study. Alimentary Pharmacology and Therapeutics 25: 273–85. Silano M, Volta U, Mecchia AM, et al. (2007) Delayed diagnosis of coeliac disease increases cancer risk. BMC Gastroenterology 7: 8 Greco L, Veneziano A, Di Donato L, et al. (2004) Undiagnosed coeliac disease does not appear to be associated with unfavourable outcome of pregnancy. Gut 53: 149–51 Green PHR, Fleischauer AT, Bhagat G, et al. (2003) Risk of malignancy in patients with celiac disease. American Journal of Medicine 115: 191–5	

	Details	Additional comments
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?	Address Q2 after Q1
Objectives	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?	
Type of review	Intervention	
Language	English only	
Study design	Systematic review Prospective cohort study Population based screening studies	
Status	Published papers only (full text)	
Population	Children, young people and adults without a formal diagnosis of coeliac disease.	
Intervention	Active case-finding strategies (including frequency of testing)	
Comparator	No active case-finding	
Outcomes	• Risk of coeliac disease • Risk of/event rates of complications • Growth in children and young people • Resource use and cost • Health-related quality of life	
Other criteria for inclusion / exclusion of studies	Exclusion: • Case studies or case series • Non coeliac disease gluten sensitivity • Wheat allergy and sensitivity	
Search strategies	…..	
Review strategies	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.	
Identified papers	Systematic Reviews: 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 Sample of papers identified by NICE CG86: 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	

	associated with Down's syndrome: a record linkage study. Archives of Disease in Childhood 89: 1014–8 Bonamico M, Pasquino AM, Mariani P, et al. (2002) Prevalence and clinical picture of celiac disease in Turner syndrome. Journal of Clinical Endocrinology and Metabolism 87: 5495–8 Francis J, Carty JE, Scott BB (2002) The prevalence of coeliac disease in rheumatoid arthritis. European Journal of Gastroenterology and Hepatology 14: 1355–6 Bonamico M, Mariani P, Danesi HM, et al. (2001) Prevalence and clinical picture of celiac disease in Italian Down syndrome patients: a multicenter study. Journal of Pediatric Gastroenterology and Nutrition 33: 139–43 George EK, Hertzberger-Ten Cate R, Suijlekom-Smit LW, et al. (1996) Juvenile chronic arthritis and coeliac disease in The Netherlands. Clinical and Experimental Rheumatology 14: 571–5

	Details	Additional comments
Review question 5.1	What is the sensitivity and specificity of the serological tests for coeliac disease? Are the sensitivity and specificity results different in any specified subgroups?	
Objectives	To determine the accuracy of the different serological tests for coeliac disease and any subgroups of people for whom the accuracy varies.	
Type of review	Diagnostic test accuracy	
Language	English only	
Study design	Systematic review Test-and-treat RCT Cross-sectional study If insufficient evidence is identified, will also include: Cohort study Case-control	
Status	Published papers only (full text)	
Population	Children, young people and adults with suspected coeliac disease.	
Index test	Serological tests: • Immunoglobin A tissue transglutaminase antibodies (IgA tTGA) • Immunoglobin A endomysial antibodies (IgA EMA) • Immunoglobin G tissue transglutaminase antibodies (IgG tTGA) • Immunoglobin G endomysial antibodies (IgG EMA) • Human leukocyte antigen (HLA) DQ2/DQ8 testing • Deamidated gliadin peptide (DGP) antibodies	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)
Reference standard	Intestinal biopsy *(Head to head comparisons of different serological tests against intestinal biopsy)*	Exclude capsule biopsy
Outcomes	Clinical utility or diagnostic test accuracy (if available) including: • Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio, and area under the ROC analyses. • Test validity such as face validity, content validity, construct validity, concurrent validity, criterion validity; • Test reliability such as internal reliability/consistency, test-retest reliability, inter-rater reliability. Health-related quality of life Resource use and cost	
Other criteria for inclusion / exclusion of studies	Exclusion: • Self-diagnosis kits • Point of care testing • Immunoglobin G antigliadon antibody (IgG AGA) • Immunoglobin A antigliadon antibody	

	(IgA AGA)	
Search strategies	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
Review strategies	QUADAS-2 tool 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. 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. All key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. Sub-analysis will be undertaken by subgroups of patients where appropriate	

Identified papers	Systematic Reviews: 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 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 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 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 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). 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) Sample of papers identified in NICE CG86: 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 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 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 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 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 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

	Details	Additional comments
Review question 5.2	Which serological test is the most appropriate to diagnose coeliac disease? Depending on test results, should more than one test be used and, if so, what should be the sequence of testing? Following which sequence of tests and test results is it appropriate to refer onwards for endoscopic intestinal biopsy for confirmatory diagnosis?	
Objectives	To determine when: 1. serological test results indicate a diagnosis of coeliac disease without need for intestinal biopsy 2. serological test results indicate a referral for intestinal biopsy for confirmatory diagnosis is appropriate.	
Type of review	Diagnostic (Diagnostic strategy/pathway)	Diagnostic strategy/pathway that involves parallel or sequential/serial testing
Language	English only	
Study design	Systematic review Test-and-treat RCT Cross-sectional study If insufficient evidence is identified, will also include: Cohort study Case-control	
Status	Published papers only (full text)	
Population	Children, young people and adults with suspected coeliac disease.	
Index test	Combinations (parallel or sequential) of serological and IgA deficiency testing Various criteria for referral to a gastrointestinal specialist for intestinal biopsy for confirmatory diagnosis following serological and IgA deficiency testing	
Reference standard(s)	Intestinal biopsy Standard serological and IgA deficiency test algorithms, including test algorithm in NICE CG86.	Exclude capsule biopsy. Testing algorithm in NICE CG86: • IgA tTGA as first line test • IgA EMA if above is equivocal • IgA deficiency testing if either above are negative • IgG tTGA and/or IgG EMA if confirmed IgA deficiency • Referral if any tTGA or EMA test above is positive.
Outcomes	Clinical utility or diagnostic test accuracy (if available) including: • Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio and area under the ROC analyses. • Test validity such as face validity, content validity, construct validity, concurrent validity, criterion validity; • Test reliability such as internal reliability/consistency, test-retest reliability, inter-rater reliability. Health-related quality of life	

	Resource use and cost	
Other criteria for inclusion / exclusion of studies	Exclusion: • Self-diagnosis kits • Point of care testing • Immunoglobin G antigliadon antibody (IgG AGA) • Immunoglobin A antigliadon antibody (IgA AGA)	
Search strategies	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
Review strategies	QUADAS-2 tool 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 key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements. Sub-analysis will be undertaken by subgroups of patients where appropriate	
Identified papers	<u>Systematic Reviews:</u> 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) Alimentary Pharmacology and Therapeutics.2006;24(1):47-54 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 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 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 <u>Sample of papers identified in NICE CG86:</u> 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. Clinical Gastroenterology and Hepatology 6: 314–20	

	Details	Additional comments
Review question 5.3	What are the referral indications for endoscopic intestinal biopsy for further investigation in people with coeliac disease?	
Objectives	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.	
Type of review	Prognostic	
Language	English only	
Study design	No restriction (except qualitative studies and case reports)	
Status	Published (full text only)	
Population	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.
Prognostic factor	Indications (other than the sequence of serological testing [question 4]) may indicate appropriate referral for endoscopic intestinal biopsy	
Comparator	Not applicable	
Outcomes	• Complications of coeliac disease • Mortality • Health related quality of life • Resource use and cost	Complications include, but are not limited to: • osteoporosis • ulcerative jejunitis • malignancy (intestinal lymphoma) • functional hyposplenism • vitamin D deficiency • iron deficiency • auto-immune diseases
Other criteria for inclusion / exclusion of studies	Exclusion : • Non coeliac disease gluten sensitivity • Studies examining clinical utility of serological testing • Wheat allergy and sensitivity • Use of intestinal biopsy for initial diagnosis • Aspects related to routine monitoring (this is covered in question 7)	
Search strategies	…….	
Review strategies	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 key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.	
Identified papers	None.	

	Details	Additional comments
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?	
Objectives	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.	
Type of review	Intervention	
Language	English only	
Study design	Systematic review RCTs If insufficient evidence is identified, will also include: Non-randomised controlled trials Prospective cohort study	
Status	Published (full text only)	
Population	Children, young people and adults with coeliac disease	
Intervention	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
Comparator	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)	
Outcomes	• Resolution of gastrointestinal and non-gastrointestinal symptoms • Growth in children and young people • Complications of coeliac disease • Dietary adherence • Impact on carers • Health-related quality of life •	Complications include: • osteoporosis • ulcerative jejunitis • malignancy (intestinal lymphoma) • functional hyposplenism • vitamin D deficiency • iron deficiency • auto-immune diseases
Other criteria for inclusion / exclusion of studies	Exclusion: • Case series and case studies • Non coeliac disease gluten sensitivity • Wheat allergy or sensitivity	
Search strategies	…….	
Review	Appropriate NICE Methodology Checklists,	

strategies	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. Sub-analysis will be undertaken for people at risk of developing complications; adults vs. children, if appropriate.	
Identified papers	For a): Studies 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, For b): Studies 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 & Therapeutics, 08 2008, vol./is. 28/3(364-70), 0269-2813;0269-2813	

	Details	Additional comments
Review question 6.1	a) What are the potential causes of non-responsive coeliac disease?	This question will identify the proportion of patients with non-responsive disease who fall into each of the following categories: Continued ingestion of gluten • Poor compliance • Inadvertent (contamination) Co-existing conditions: • Lactose or fructose intolerance • Other food intolerances • Pancreatic insufficiency • Microscopic colitis • Bacterial overgrowth • Collagenous colitis or collagenous sprue • Irritable bowel syndrome • Ulcerative jejunitis • Enteropathy (including autoimmune enteropathy) • associated T-cell lymphoma • Functional disorders • Common variable immunodeficiency Refractory coeliac disease
Objectives	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	
Type of review	Prevalence	
Language	English only	
Study design	Systematic review Case series Cross-sectional study	
Status	Published (full text only)	
Population	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
Index test(s)	Not relevant	
Reference standard(s)	Not relevant	
Outcomes	Proportion of differing causes of non-responsiveness, which should be considered as part of the differential diagnosis of non-responsive coeliac disease	
Other criteria for inclusion / exclusion of studies	Exclusion: Non biopsy confirmed Symptoms persisting less than 6 months No health care professional advice on gluten free	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	
Search strategies	…….	
Review strategies	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 key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.	
Identified papers	Studies O'Shea, Abuzakouk, O'Morain et al (2008) Investigation of molecular markers in the diagnosis of refractory coeliac disease in a large patient cohort. Journal of Clinical Pathology, 11 2008, vol./is. 61/11(1200-2), 0021-9746;1472-4146 Barret, Malamut, Rahmi et al (2012) Diagnostic yield of capsule endoscopy in refractory celiac disease. American Journal of Gastroenterology, 10 2012, vol./is. 107/10(1546-53), 0002-9270;1572-0241 Van Weyenberg, Meijerink, Jacobs et al (2011) MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system. Radiology, 04 2011, vol./is. 259/1(151-61), 0033-8419;1527-1315	

	Details	Additional comments
Review question 6.1	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	This question will inform how to investigate patients with suspected refractory coeliac disease Tests that will guide the ongoing clinical management, such as assessing the risk of lymphoma
Objectives	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	
Type of review	Intervention	
Language	English only	
Study design	Systematic review Test-and-Treat RCT Cross-sectional study If insufficient evidence is identified, will also include: Cohort study Case-control	
Status	Published (full text only)	
Population	Patients with a confirmed diagnosis of coeliac disease, *in whom persistent villous atrophy is found on biopsy.* 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
Intervention	Investigative tests: • Clonality assessment • Flow cytometry • Aberrant T cell assessment • Immunophenotyping • Imaging	
Comparator	Do nothing	
Outcomes	Clinical utility: • Change to clinical management • Resource use and cost • Patient outcomes at follow up • Health-related quality of life	
Other criteria for inclusion / exclusion of studies	Exclusion: None	
Search strategies	…….	
Review strategies	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 key outcomes from evidence will be presented in modified GRADE profiles and further summarised in evidence statements.	
Identified papers	Studies O'Shea, Abuzakouk, O'Morain et al (2008) Investigation of molecular markers in the diagnosis of refractory coeliac disease in a large patient cohort. Journal of Clinical Pathology, 11 2008, vol./is. 61/11(1200-2), 0021-9746;1472-4146 Barret, Malamut, Rahmi et al (2012) Diagnostic yield of capsule endoscopy in refractory celiac disease. American Journal of Gastroenterology, 10 2012, vol./is. 107/10(1546-53), 0002-9270;1572-0241 Van Weyenberg, Meijerink, Jacobs et al (2011) MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system. Radiology, 04 2011, vol./is. 259/1(151-61), 0033-8419;1527-1315	

	Details	Additional comments
Review question 6.2	What is the effectiveness of pharmacological treatments for people with refractory coeliac disease?	
Objectives	To determine what medication can help treat coeliac disease that is not responding to dietary management and when other diagnoses have been excluded.	
Type of review	Intervention	
Language	English only	
Study design	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
Status	Published (full text only)	
Population	Children, young people and adults with refractory coeliac disease	
Intervention	Pharmacological treatments for refractory coeliac disease which include, but are not limited to: • Anti-TNF (including infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira], golimumab [Simponi], certolizumab [Cimzia]) • ASA preparation/Mesalazine/Mesalamine (Apriso, Asacol, Canasa, Lialda, pentasa, Rowasa) • Azathioprine (Imuran) • Prednisolone (Ak-Pred, Articulose-50, AsmalPred Plus, Delta-Cortef, Econopred, etc) • Budesonide (Entocort, Pulmicort, Rhinocort, Symbicort) • Cladribine (Leustatin) • Cyclosporin (Gengraf, Neoral, Restasis, Sandimmune) • Thioguanine (Tabloid) • Other corticosteroids (other than prednisolone and budesonide)	
Comparator	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.
Outcomes	• Resolution of gastrointestinal and non-gastrointestinal symptoms • Complications of coeliac disease • Adverse effects • Health-related quality of life • Impact on carers • Serological response • Histological response •	Complications include, but are not limited to: • osteoporosis • ulcerative jejunitis • malignancy (intestinal lymphoma) • functional hyposplenism • vitamin D deficiency • iron deficiency • auto-immune diseases
Other criteria for inclusion / exclusion of studies	Exclusion: • Case reports	

Search strategies	…….	
Review strategies	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.	
Identified papers	Studies Tack, Verbeek, Al-Toma et al (2011) Evaluation of Cladribine treatment in refractory celiac disease type II. World Journal of Gastroenterology 17(4): 506–513. Jamma, Leffler, Dennis et al (2011) Small intestinal release mesalamine for the treatment of refractory celiac disease type I. Journal of Clinical Gastroenterology, 01 2011, vol./is. 45/1(30-3), 0192-0790;1539-2031 Brar, Lee, Lewis et al (2007) Budenoside in the treatment of refractory celiac disease. American Journal of Gastroenterology, 10 2007, vol./is. 102/10(2265-9), 0002-9270;0002-9270 Al-Toma, Verbeek, Hadithi et al (2007) Survival in refractory coeliac disease and enteropathy –associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut, 10 2007, vol./is. 56/10(1373-8), 0017-5749;0017-5749 Goerres, Meijer, Wahab et al (2003) Azathioprine and prednisone combination therapy in refractory coeliac disease. Alimentary Pharmacology & Therapeutics, 09 2003, vol./is. 18/5(487-94), 0269-2813;0269-2813	

	Details	Additional comments
Review question 6.3	What is the effectiveness of nutritional management or nutritional support for people with refractory coeliac disease?	
Objectives	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.	
Type of review	Intervention	
Language	English only	
Study design	Systematic review RCTs If insufficient evidence is identified, will also include: Non-randomised controlled trials Prospective cohort study	
Status	Published (full text only)	
Population	Children, young people and adults with refractory coeliac disease	
Intervention	Nutritional support for people with refractory coeliac disease which includes, but is not limited to: • Further dietary exclusions • Oral nutrition support (for example, fortified food) • Enteral tube feeding (delivery of nutrition into the gut) • Parenteral nutrition (delivery of nutrition intravenously)	Further dietary exclusions could include high allergenic foods such as soya, milk, egg, etc
Comparator	Standard care Placebo Head to head comparison	
Outcomes	• Resolution of gastrointestinal and non-gastrointestinal symptoms • Complications of coeliac disease • Adverse events • Health-related quality of life • Impact on carers • Serological response	Complications include, but are not limited to: • osteoporosis • ulcerative jejunitis • malignancy (intestinal lymphoma) • functional hyposplenism • vitamin D deficiency • iron deficiency • auto-immune diseases
Other criteria for inclusion / exclusion of studies	Exclusion: • Retrospective cohort study, case series and case reports.	
Search strategies	……	
Review strategies	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.	
Identified papers	Studies Jamma, Rubio-Tapia, Kelly et al (2010) Celiac crisis is a rare but serious complication of celiac disease in adults. Clinical Gastroenterology & Hepatology, 07 2010, vol./is. 8/7(587-90), 1542-3565;1542-7714	

	Details	Additional comments
Review question 6.4	What is the effectiveness of autologous stem cell transplant for people with refractory coeliac disease?	
Objectives	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.	
Type of review	Intervention	
Language	English only	
Study design	No restriction except qualitative studies and case reports.	
Status	Published (full text only)	
Population	Children, young people and adults with refractory coeliac disease	
Intervention	Chemotherapy followed by autologous stem cell transplant	
Comparator	Standard care Placebo Head to head comparison with pharmacological treatments	
Outcomes	• Health-related quality of life • Impact on carers • Resolution of gastrointestinal and non-gastrointestinal symptoms • Complications of coeliac disease • Complications from surgery • Serological response • Adverse events	Complications include, but are not limited to: • osteoporosis • ulcerative jejunitis • malignancy (intestinal lymphoma) • functional hyposplenism • vitamin D deficiency • iron deficiency • auto-immune diseases
Other criteria for inclusion / exclusion of studies	Exclusion: • Qualitative studies and case reports	
Search strategies	……	
Review strategies	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.	
Identified papers	None identified	

	Details	Additional comments
Review question 7.1	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? 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?	
Objectives	To establish what information is needed by patients to: • help decide whether to be tested for coeliac disease • manage their diet before being tested	
Type of review	Information and support	
Language	English only	
Study design	No restriction except case reports	
Status	Published (full text only)	
Population	Children, young people and adults being investigated for coeliac disease	
Intervention	Information strategies to help people decide whether to be tested for coeliac disease Information to help people to manage their diet prior to the tests (to improve the accuracy of the tests).	Information needs may be different (and include more specific information) for patients at higher risk and some of these patients may be asymptomatic
Comparator	N/A	
Outcomes	Any information identified Patient experience Resource use and cost	
Other criteria for inclusion / exclusion of studies	Case reports	
Search strategies	Date restriction: 2008 onwards	To limit the amount of sifting required, the last guideline was used to identify relevant studies published prior to 2008
Review strategies	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. Separate analysis will be performed where appropriate for parents and carers.	
Identified papers	None.	

	Details	Additional comments
Review question 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?	
Objectives	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. To elicit preferences of patients to improve their self-management including information, different monitoring strategies, and with who they are followed up.	
Type of review	a) Intervention (for effectiveness of any educational or support programmes/strategies to improve adherence) b) Qualitative (patient experiences about required information and monitoring strategies to improve self-management including adherence)	
Language	English only	
Study design	a) Systematic review RCTs Prospective cohort studies b) No restriction except case reports	
Status	Published (full text only)	
Population	Children, young people and adults with coeliac disease	
Intervention	a) Any educational or support programmes/strategies to improve adherence b) Any information needs identified	
Comparator	a) Standard care b) N/A	
Outcomes	• Resolution of gastrointestinal and non-gastrointestinal symptoms • Patient experience • Complications of coeliac disease • Resource use and cost • Adherence • Health-related quality of life • Impact on carers •	
Other criteria for inclusion / exclusion of studies	Exclusion: • Non coeliac disease gluten sensitivity • Wheat allergy and sensitivity	

Search strategies	……..	
Review strategies	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. Separate analysis will be performed where possible for parents and carers.	
Identified papers	None.	

	Details	Additional comments
Review question 7.3	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?	
Objectives	To determine what other dietary management strategy/advice should be given to people with coeliac disease.	
Type of review	Intervention	
Language	English only	
Study design	Systematic reviews RCTs If insufficient evidence is identified, will also include: Non-randomised controlled trials Prospective cohort studies	
Status	Published (full text only)	
Population	Children, young people and adults with coeliac disease	
Intervention	a) Any dietary management/advice other than a gluten-free diet The use of nutritional supplements as 'other dietary advice' will only include: • calcium • Vitamin D • Vitamin B12 • Iron • Folic acid b) Use of gluten-free oats as part of the exclusion diet (including thresholds for oats intake)	
Comparator	Gluten free diet only (standard care)	
Outcomes	• Resolution of gastrointestinal and non-gastrointestinal symptoms • Growth in children and young people • Complications of coeliac disease • Dietary adherence • Impact on carers • Health-related quality of life • Serological response • Histological response	Complications include, but are not limited to: • osteoporosis • ulcerative jejunitis • malignancy (intestinal lymphoma) • functional hyposplenism • vitamin D deficiency • iron deficiency • auto-immune diseases
Other criteria for inclusion / exclusion of studies	Exclusion: • Case series and case studies • Non coeliac disease gluten sensitivity • Wheat allergy and sensitivity	
Search strategies	…….	
Review strategies	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.	
Identified papers	Systematic Reviews: Pulido OM, Gillespie Z, Zarkadas M, et al. (2009) Introduction of oats in the diet of individuals with celiac disease: a systematic review. Advances in Food and Nutrition Research 57(6):235-285 Haboubi, Taylor and Jones (2006) Coeliac disease and oats: a systematic review. Postgraduate Medical Journal.2006;82(972):672-678 Studies Villaneuva, Maranda and Nwosu (2012) Is vitamin D deficiency a feature of pediatric celiac disease? Journal of Pediatric Endocrinology, 2012, vol./is. 25/5-6(607-10), 0334-018X;0334-018X (2012) Hadithi, Mulder, Stam et al (2009) Effect of B vitamin supplementation on plasma homocysteine levels in celiac disease. World Journal of Gastroenterology, 02 2009, vol./is. 15/8(955-60), 1007-9327;1007-9327 Mager, Qiao and Turner (2012) Vitamin D and K status influences bone mineral density and bone accrual in children and adolescents with celiac disease. European Journal of Clinical Nutrition, 04 2012, vol./is. 66/4(488-95), 0954-3007;1476-5640 Hallert, Grant, Grehn et al (2002) Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. Alimentary Pharmacology & Therapeutics, 07 2002, vol./is. 16/7(1333-9), 0269-2813;0269-2813.	