Crohn’s disease

Evidence Update September 2014

A summary of selected new evidence relevant to NICE clinical guideline 152 ‘Crohn’s disease: management in adults, children and young people’ (2012)

Evidence Update 65
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Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

Crohn’s disease, NICE clinical guideline 152 (2012)

A search was conducted for new evidence from 13 March 2012 to 16 April 2014. A total of 3197 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 39 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group (EUAG), which advised on the final list of 14 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 152 (NICE CG152). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guidelines process and methods guides for further information about updating clinical guidelines.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

Osteoporosis: assessing the risk of fragility fracture, NICE clinical guideline 146 (2012)

Infliximab (review) and adalimumab for the treatment of Crohn’s disease, NICE technology appraisal guidance 187 (2010)

NICE-accredited guidance
NICE Pathways

NICE pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathways cover advice and recommendations related to this Evidence Update:

- [Crohn’s disease](#), NICE Pathway

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk
Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG152. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG152.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

<table>
<thead>
<tr>
<th>Key point</th>
<th>Potential impact on guidance</th>
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<tr>
<td><strong>Patient information and support</strong></td>
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<tr>
<td>• Parents of children with Crohn’s disease need information to help decide whether to start TNF inhibitor treatments. Parents have particular worries about the risk of cancer and lack of long-term safety data.</td>
<td>Yes</td>
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<td><strong>Inducing remission in Crohn’s disease</strong></td>
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<tr>
<td>• Azathioprine(^2) and mercaptopurine(^3) may not be better than placebo for inducing remission of Crohn’s disease; however infliximab plus azathioprine may be more effective than infliximab alone.</td>
<td>✓*</td>
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<tr>
<td>• Methotrexate(^4) may not be effective for inducing remission in Crohn’s disease, and infliximab plus methotrexate may not be more effective than infliximab alone.</td>
<td>✓</td>
</tr>
<tr>
<td>• There is no evidence to suggest that naltrexone(^5) is effective for inducing remission of Crohn’s disease.</td>
<td>✓</td>
</tr>
<tr>
<td>• Adalimumab may be an effective treatment for inducing remission of Crohn’s disease in people who previously had infliximab treatment failure.</td>
<td>✓*</td>
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<tr>
<td>• People taking TNF inhibitors may be at increased risk of opportunistic infections.</td>
<td>✓</td>
</tr>
<tr>
<td>• The presence of antibodies against TNF inhibitors is associated with loss of response to treatment and lower trough levels of the drug in blood serum.</td>
<td>✓</td>
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\(^2\) At the time of publication of this Evidence Update, not all azathioprine products had UK marketing authorisation for this indication, please see the summary of product characteristics for each drug formulation.

\(^3\) At the time of publication of this Evidence Update, mercaptopurine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

\(^4\) At the time of publication of this Evidence Update, methotrexate did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

\(^5\) At the time of publication of this Evidence Update, naltrexone did not have UK marketing authorisation for this indication and was not considered for NICE CG152.

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.
## Key point

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### Maintaining remission in Crohn’s disease

- Thiopurine treatment may be feasible in people who previously stopped treatment with these drugs because of adverse events. However, rare but serious adverse events, such as pancreatitis or bone marrow failure, may reoccur.

### Maintaining remission in Crohn’s disease after surgery

- Adalimumab may be more effective than azathioprine or mesalazine\(^6\) in maintaining remission of Crohn’s disease after surgery.

### Monitoring for osteopenia and assessing fracture risk

- Low BMI may be the most important risk factor for osteoporosis in people with Crohn’s disease.

### Conception and pregnancy

- TNF inhibitors do not seem to be associated with major adverse effects when used during pregnancy, but infants exposed to these drugs in utero may be at increased risk of adverse reactions to live vaccines.

- Thiopurine use in pregnancy may be associated with preterm birth, but may not be associated with low birth weight or congenital malformations.

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\(^6\) At the time of publication of this Evidence Update, mesalazine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.
1 Commentary on new evidence

These commentaries focus on the ‘key references’ identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from NICE CG152.

1.1 Patient information and support

Parents’ needs for information about tumour necrosis factor (TNF) inhibitors

NICE CG152 recommends discussing the possible nature, frequency and severity of side effects of drug treatment with people with Crohn's disease, and/or their parents or carers if appropriate.

Lipstein et al. (2013) conducted a US qualitative study in parents (n=35) of children with Crohn’s disease (n=15) or juvenile idiopathic arthritis (n=20) who had considered treatment with TNF inhibitors. Interviews were conducted either by telephone or in person and focused on parents’ discussions with treatment providers, factors considered in the decision, and information used. Recruitment continued until no new themes were discussed after 3 consecutive interviews in each disease.

Children with Crohn’s disease had tried other medications before TNF inhibitors were discussed, and most eventually received treatment with infliximab. Parents reported that the choice to use TNF inhibitors was the most difficult Crohn’s disease-related decision. The severity of disease and quality of life of their children were weighed against the risk of lymphoma and lack of long-term data for TNF inhibitors. Parents were usually introduced to the idea of TNF inhibitors by treatment providers and then sought further information to help with their decision. Parents felt that they had no choice but to try TNF inhibitors because other treatments did not work.

Several sources were used, most often verbal and written information from the care team. Another key source of information was the internet, both for general medical sites and disease-specific sites. Some parents also looked for scientific reports, such as from MEDLINE. Most parents thought that information from the internet was helpful and positive. Some sources, such as pharmaceutical companies, were thought to be biased but still made parents feel better. A final source of information was other people: friends and family with the disease or who worked in the medical profession.

Parents did not always understand the common treatment pathways or how treatment may be escalated before their child needed TNF inhibitors. Additional information on the efficacy of TNF inhibitors, how long they would take to work and long-term outcomes was also desired. The risk of cancer worried parents most, as shown by their emotions when discussing cancer risk and the frequency it was mentioned.

The study may be limited by recall bias because parents were interviewed at variable times after the treatment decision. The investigators also noted difficulty in finding parents who were in the process of deciding about TNF inhibitors or those who had declined this treatment. This may partly be explained by the relative ease of identifying via registries families who chose to start treatment. In addition, treatment with TNF inhibitors may eventually be accepted by a high proportion of families.

This study suggests that parents of children with Crohn’s disease need information to help decide whether to start TNF inhibitor treatments. Parents have particular worries about the risk of cancer and lack of long-term safety data. These findings are consistent with the
recommendation in NICE CG152 to discuss side effects of drug treatment with patients or their parents or carers.

Key reference

1.2 Inducing remission in Crohn’s disease

Infliximab combination therapy
NICE CG152 states ‘do not offer azathioprine7, mercaptopurine8 or methotrexate9 as monotherapy to induce remission’. However, azathioprine or mercaptopurine may be considered in addition to a conventional glucocorticosteroid or budesonide10 to induce remission of Crohn’s disease if there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered. Methotrexate may be added to a conventional glucocorticosteroid or budesonide in people who cannot tolerate azathioprine or mercaptopurine, or in whom thiopurine methyltransferase (TPMT) activity is deficient. See NICE CG152 for the full recommendations on azathioprine, mercaptopurine and methotrexate.

NICE technology appraisal guidance 187 (NICE TA187) recommends infliximab and adalimumab, within their licensed indications, as treatment options for adults with severe active Crohn’s disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. See NICE TA187 for the full recommendations on infliximab and adalimumab in Crohn’s disease.

Azathioprine plus infliximab
Chande et al. (2013) conducted a Cochrane review of 13 trials (n=1211) of azathioprine or mercaptopurine for induction of remission in Crohn’s disease. Included studies assessed the antimetabolite drugs azathioprine or mercaptopurine against a placebo or active comparator. Patients were adults who had acute inflammatory Crohn’s disease, defined as the presence of moderate-to-severe symptoms, a Crohn’s Disease Activity Index (CDAI) score higher than 150 or a Harvey–Bradshaw Index score of 7 or more.

There was no significant difference between the 2 antimetabolite drugs (48%) and placebo (37%) for the remission of Crohn’s disease (risk ratio [RR]=1.23, 95% confidence interval [CI] 0.97 to 1.55, p=0.084; 5 studies, n=380). No significant differences in adverse events, serious adverse events, or withdrawals due to adverse events were identified.

7 At the time of publication of this Evidence Update, not all azathioprine products had UK marketing authorisation for this indication, please see the summary of product characteristics for each drug formulation.
8 At the time of publication of this Evidence Update, mercaptopurine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
9 At the time of publication of this Evidence Update, methotrexate did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
10 At the time of publication of this Evidence Update, budesonide did not have UK marketing authorisation specifically for children and young people. Informed consent should be obtained and documented.
Azathioprine was associated with significantly lower rates of remission (32%) than infliximab (48%, RR=0.66, 95% CI 0.51 to 0.87, p=0.0029; 1 study, n=339). No significant difference in adverse events (about 90% of both groups), serious adverse events (27% on azathioprine and 24% on infliximab), or withdrawals due to adverse events (26% on azathioprine and 18% on infliximab) was identified. Azathioprine plus infliximab was associated with significantly greater rates of remission (60%) than infliximab alone (48%, RR=1.26, 95% CI 1.03 to 1.54, p=0.023; 1 study, n=338) and with a significantly lower rate of serious adverse events (15%) compared with infliximab alone (24%, RR=0.63, 95% CI 0.41 to 0.98, p=0.041; 1 study, n=338). No significant difference in overall adverse events (about 90% in both groups) or withdrawals due to adverse events (21% on azathioprine plus infliximab and 18% on infliximab alone) was identified.

The quality of the included evidence was generally rated as moderate, mainly because of sparse data. The authors noted that in almost all placebo-controlled studies all patients received steroids in addition to their randomised intervention. Therefore the remission rates in both active and placebo groups were probably due to the steroids. The authors noted that further trials of infliximab plus antimetabolites were needed to evaluate efficacy and to investigate whether antimetabolites have a role in reducing the formation of antibodies against TNF inhibitors.

This Cochrane review suggests that azathioprine and mercaptopurine may not be better than placebo for inducing remission of Crohn’s disease; however infliximab plus azathioprine may be more effective than infliximab alone. The findings on azathioprine and mercaptopurine monotherapy are consistent with NICE CG152. The results for infliximab and azathioprine combination therapy may have a potential impact on NICE CG152, which currently has no recommendation about using infliximab in combination therapy. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Key reference
Chande N, Tsoulis DJ, MacDonald JK (2013) Azathioprine or 6-mercaptopurine for induction of remission in Crohn’s disease. Cochrane Database of Systematic Reviews issue 4: CD000545

Methotrexate plus infliximab
McDonald et al. (2014) conducted a Cochrane review of 7 randomised controlled trials (RCTs; n=495) of methotrexate compared with placebo or active control for remission of Crohn’s disease. Participants in included studies were adults with active Crohn’s disease, defined as a CDAI score higher than 150. The primary outcome was the proportion of patients who were not in clinical remission and had not stopped steroids. Differences in participants, interventions and outcomes of included studies meant that pooling the data for meta-analysis was inappropriate.

In 2 small studies of low-dose oral methotrexate (n=85), remission rates did not differ significantly from placebo. A single study found that intramuscular methotrexate 25 mg per week (n=141) was significantly better than placebo for remission of Crohn’s disease (RR=0.75, 95% CI 0.61 to 0.93). In 2 small single studies of methotrexate compared with active control for remission of Crohn’s disease, methotrexate did not differ significantly from either mercaptopurine (n=58) or azathioprine (n=54). In 2 trials of infliximab (n=145), the addition of methotrexate had no significant effect on remission over that of infliximab alone.

Included trials were assessed to be at low risk of bias on most criteria. However, 4 studies did not report the method of allocation concealment, and 3 were not double-blind. The authors noted that larger trials of low-dose oral methotrexate may be justified.

A randomised controlled trial (n=126) by Feagan et al. (2014) also compared infliximab plus methotrexate with infliximab alone in people with Crohn’s disease and who had steroid treatment, specifically prednisone, in the 6 weeks before randomisation. Patients who
previously received infliximab were excluded, as were those who previously had ineffective methotrexate treatment. Additional exclusion criteria included risk factors for infliximab toxicity and treatment with azathioprine or mercaptopurine in the previous 8 weeks. The primary endpoint was time to treatment failure, defined as not having prednisone-free remission at week 14 or not maintaining remission until week 50.

Participants were allocated by computerised randomisation to infliximab plus intramuscular methotrexate or infliximab plus intramuscular placebo. Dose escalation was used for methotrexate (from 10 mg/week to 25 mg/week), for a total of 5 weeks. Infliximab was dosed at 5 mg/kg at all times, but time between doses was increased from once every 3 weeks to once every 8 weeks, for a total of 46 weeks. An intravenous 200 mg dose of hydrocortisone was given 30 minutes before each infusion of infliximab. Participants stopped the trial if they had no response by week 14.

No significant differences were seen in time to treatment failure between groups (hazard ratio [HR]=1.16, 95% CI 0.62 to 2.17). A regression analysis adjusted for C-reactive protein concentration, CDAI score, prednisone dose, and time since diagnosis confirmed the lack of difference between treatments (HR=1.35, 95% CI 0.68 to 2.67). Subgroup analysis also showed no significant difference between treatments for participants who had a diagnosis of Crohn’s disease for less than 2 years or had a C-reactive protein concentration of more than 4 mg/litre.

The most common severe adverse event was worsening of Crohn’s disease (8 patients). Methotrexate pneumonitis occurred in 1 patient, and 14 patients had abnormal serum aminotransferase results. No clinically relevant hepatotoxicity was recorded.

The authors considered potential weaknesses of their study to be: not including a prednisone monotherapy arm; that steroid therapy was started at the discretion of the investigator; and that Crohn’s disease activity was not confirmed by colonoscopy.

These studies suggest that methotrexate may not be effective for inducing remission in Crohn’s disease, and infliximab plus methotrexate may not be more effective than infliximab alone. This evidence is unlikely to have an impact on NICE CG152.

Key references


Naltrexone

NICE CG152 does not include recommendations on naltrexone for Crohn’s disease. At the time of publication of this Evidence Update naltrexone did not have UK marketing authorisation for this indication.

Segal et al. (2014) conducted a Cochrane review of RCTs of low-dose naltrexone for inducing remission in Crohn’s disease. Participants in included trials were of any age, with active Crohn’s disease defined by clinical, radiographic, endoscopic, and histological criteria.

No significant difference between naltrexone and placebo for remission of Crohn’s disease was seen in 1 trial in adults (n=34) or in 1 trial in children (n=12). The included studies were assessed to be at low risk of bias, but the overall quality of the studies was considered to be low because of serious imprecision.

There is no evidence to suggest that naltrexone is effective for inducing remission of Crohn’s disease, therefore no impact on NICE CG152 is expected.
Key reference

Adalimumab after failure of infliximab

NICE CG152 does not include recommendations about use of an alternative TNF inhibitor after treatment with a TNF inhibitor has failed.

Da et al. (2013) conducted a systematic review of studies that assessed adalimumab treatment in people with Crohn’s disease who had previously tried infliximab but had experienced treatment failure. Studies were included if they used only subjective measures of efficacy or did not specify the reason for stopping infliximab treatment. Overall 10 studies including 1009 people were included in the review; however, only 1 study was an RCT, the rest were open-label cohort studies.

Luminal disease remission was reported in 8 studies, defined as a CDAI score of less than 150 (6 studies), or a Harvey–Bradshaw Index score of 4 or less (1 study) or less than 5 (1 study). Seven studies reported on fistulising disease, and all but 1 of these defined remission as complete closure of all fistulas. The main reason for discontinuation of infliximab was loss of response in 6 trials, hypersensitivity in 3 trials, and intolerance in 1 study. Six studies used initial adalimumab doses of 160 mg at week 0 and 80 mg at week 2, the other 4 studies used 80 mg at week 0 and 40 mg at week 2. Maintenance dosing was 40 mg every 2 weeks in 9 studies, with the other study using a maintenance dose of 80 mg.

During the induction phase (first 4 weeks), remission rates for luminal disease with adalimumab ranged from 12% to 67%. In the placebo-controlled trial (n=325), the remission rate in the induction phase was 21% with adalimumab and 7% with placebo. In the maintenance phase, remission with adalimumab ranged from 29% to 72%. For fistulising disease, remission in the induction phase ranged from 5% to 50% with adalimumab. The remission rate in the 1 RCT was 4% for adalimumab and 8% for placebo (n=325). In the maintenance phase, remission rates for fistulising disease ranged from 27% to 68%. Adverse events occurred in 13–69% of participants, although in 8 of the 10 studies 4% (or less) of participants discontinued adalimumab because of adverse events (range 0–14%).

This systematic review was limited by the lack of statistical analysis of the results. Differences in study populations, length of study and dosing may have made pooling and meta-analysis inappropriate, but the authors did not explain why they chose to present results simply as ranges. The authors noted that the best results seemed to be from studies that recruited participants with less severe disease.

Additionally, the only RCT included had the lowest remission rates; the authors of the review noted that this trial did not show a significant difference from placebo. However, this RCT reported results only for 4 weeks. Many of the open-label cohort studies showed increases in remission from the induction to the maintenance phase, so the RCT may have stopped before the final effects were known.

The authors further noted that the remission rates in the open-label cohort studies they included were higher than remission rates in trials of adalimumab that compared treatment in people who had never had infliximab with those who had previously used infliximab. The effects in those with previous infliximab use ranged from 31% to 42%. The high response rates in this review (up to 68%) suggest the possibility of bias in the cohort studies from their open-label nature or from how they selected participants. However, this systematic review did not report a quality assessment of the included studies.

Although high-quality confirmatory studies are needed, this systematic review suggests that adalimumab may be an effective treatment for inducing remission of Crohn’s disease in
people who previously had infliximab treatment failure. This result could have a potential impact on NICE CG152, which does not include recommendations on alternative TNF inhibitor treatment after failure of another TNF inhibitor. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

**Key reference**

**Opportunistic infections associated with TNF inhibitors**

NICE CG152 does not include recommendations about opportunistic infections associated with TNF inhibitor use. The summary of product characteristics for infliximab and adalimumab note that patients must be monitored closely for infections, including tuberculosis, before, during and after treatment.

Ford et al. (2013) did a systematic review and meta-analysis of RCTs (n=7045) of TNF inhibitors in inflammatory bowel disease to assess the occurrence of opportunistic infections. In total, 22 placebo-controlled RCTs were included, 15 of which were in people with Crohn’s disease; the rest were studies in people with ulcerative colitis. The duration of follow-up of studies ranged from 2 weeks to 56 weeks.

Overall, 4135 people (59%) with inflammatory bowel disease were randomised to TNF inhibitors and 2919 people (41%) were randomised to placebo. People allocated to TNF inhibitors had 39 opportunistic infections (0.9%) and those allocated to placebo had 9 opportunistic infections (0.3%). Opportunistic infections recorded were *Mycobacterium tuberculosis*, oral or oesophageal candidiasis, varicella-zoster, herpes zoster, Epstein–Barr virus or cytomegalovirus, *Nocardia*, herpes simplex, and ‘unspecified’.

The relative risk of developing an opportunistic infection was higher for people on TNF inhibitors than those on placebo (RR=2.05, 95% CI 1.10 to 3.85, p=0.02). The rate of infections did not differ significantly in subgroup analyses of the specific TNF inhibitor used, use of immunosuppressants or steroids, or trials at low versus high or unclear risk of bias. Opportunistic infection resulted in 1 death due to disseminated tuberculosis. *Mycobacterium tuberculosis* infection occurred in 8 people on TNF inhibitors and 0 people on placebo, but this difference was not significant (RR=2.52, 95% CI 0.62 to 10.21, p value not reported).

No significant heterogeneity was detected among the included trials, and the funnel plot showed no publication bias. Only 4 trials were assessed to be at low risk of bias. The authors noted that the maximum length of follow-up was 56 weeks, so the risk of opportunistic infection for longer term use remains unknown.

Evidence suggests that people taking TNF inhibitors may be at increased risk of opportunistic infections. This previously recognised finding is unlikely to have an impact on NICE CG152.

**Key reference**
Antibodies against TNF inhibitors

NICE CG152 does not include recommendations about the development of antibodies against TNF inhibitors. The summary of product characteristics for infliximab notes that patients who developed antibodies to infliximab were more likely (approximately 2–3 fold) to develop infusion-related reactions.

Nanda et al. (2013) conducted a systematic review and meta-analysis of 13 studies of infliximab in Crohn’s disease (n=1077) or ulcerative colitis (n=301) to assess serum antibodies to infliximab and their effect on clinical outcomes. The primary outcome measure was loss of response, defined as a relapse of clinical symptoms in a person who was previously in remission. No predefined CDAI score was needed to meet the definition of relapse, and studies did not need to objectively confirm active inflammation as the cause of symptoms. Antibodies to infliximab could be measured by any method.

Studies were included if they reported measures of antibodies to infliximab and either clinical outcomes or serum infliximab levels. Of 10 studies with data suitable for the immunogenicity meta-analysis, 6 were on Crohn’s disease, 1 was in ulcerative colitis, 1 study reported results for each disease separately and 2 reported pooled results for inflammatory bowel disease.

People with Crohn’s disease had a higher likelihood of loss of response if antibodies to infliximab were detected (RR=3.2, 95% CI 1.9 to 5.5, p<0.0001; 7 studies, n=494). However, significant heterogeneity was noted between the included studies. Excluding 2 studies reduced heterogeneity to a value that ‘might not be important’, resulting in a lower effect size (RR=2.2, 95% CI 1.5 to 3.4, p=0.0002).

Sensitivity analyses were conducted that accounted for random or fixed effects estimates, infliximab dosing schedule, type of antibody assay, or whether loss of response was defined by the clinician or by objective score on a validated tool. No sensitivity analysis significantly altered the results for the primary outcome.

Serum levels at trough (lowest point, immediately before receiving next dose) were significantly lower in people who had antibodies to infliximab than in those who did not have antibodies (standardised mean difference=−0.8, 95% CI −1.2 to −0.4, p<0.0001; 1 study in Crohn’s disease [n=58] plus 2 studies in ‘mixed inflammatory bowel disease’ [n=185]).

Formal funnel plot testing of publication bias was not done because of the low number of included studies. Only 1 study was rated as moderate quality, 7 were rated as low quality, and 5 were rated as very low quality.

Evidence suggests that the presence of antibodies against TNF inhibitors is associated with loss of response to treatment and lower trough levels of the drug in blood serum. This evidence is unlikely to have an impact on NICE CG152 because methods to improve treatment response in the presence of antibodies are unclear.

Key reference

1.3 Maintaining remission in Crohn’s disease

Adverse events associated with thiopurine treatment

NICE CG152 recommends discussing with people with Crohn's disease, and/or their parents or carers if appropriate, options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. The person’s views should be recorded in their notes.
Azathioprine\textsuperscript{11} or mercaptopurine\textsuperscript{12} should be offered as monotherapy to maintain remission, both for people who have previously received these drugs with a conventional glucocorticosteroid or budesonide to induce remission and considered in people who have not previously received these drugs.

Chaparro\textit{et al. (2013)} reported a retrospective study investigating thiopurine toxicity using a Spanish national database containing information on thiopurine prescriptions from 1973 to 2010.

Patients with inflammatory bowel disease were identified (n=3931), 69\% of whom had Crohn's disease (n=2688). Data for the number of months between starting and stopping thiopurines and treatment-related adverse events were extracted from the database. Most people (95\%) were prescribed azathioprine, with the rest prescribed mercaptopurine. The main indications for thiopurine treatment were maintenance of remission (52\% of patients), induction of remission (23\%) and prophylaxis of post-surgical recurrence of inflammatory bowel disease (11\%).

The most commonly reported adverse events were nausea (8\% of patients), hepatotoxicity (4\%), leukopenia (4.1\%), pancreatitis (4\%) and bone marrow failure (2.2\%). The mean time to onset of adverse events was 10 months (range 0–178 months, median=1 month). Cancer was noted in 7 patients, including 4 cases of lymphoma.

Adverse events led to discontinuation in 17\% of the study cohort; however; slightly more than a third (37\%) of those patients restarted thiopurine treatment. Adverse events reoccurred in 40\% of those who restarted thiopurine treatment. The reoccurrence of the same adverse event was seen in 3 of 7 patients who previously stopped treatment because of pancreatitis, 4 of 9 who had bone marrow failure and 2 of 23 people who had hepatotoxicity.

In analysis of predictive factors for adverse events, women had a slightly higher chance of any adverse event (HR=1.2, 95\% CI 1.0 to 1.4). Patients with Crohn's disease were much more likely than those with ulcerative colitis to have an adverse event (HR=10, 95\% CI 7 to 14). The authors noted that the lack of information on thiopurine methyltransferase activity (TPMT) was a limitation of their study, because this could have indicated people who were at higher risk of severe side effects.

This study suggests that thiopurine treatment may be feasible in people who previously stopped treatment with these drugs because of adverse events. However, rare but serious adverse events, such as pancreatitis or bone marrow failure, may reoccur. This evidence is consistent with NICE CG152, which recommends discussing the potential side effects of drug maintenance treatment in people whose Crohn's disease is in remission.

\textbf{Key reference}


\textbf{Maintenance treatment with adalimumab}

NICE CG152 recommends discussing with people with Crohn's disease, and/or their parents or carers if appropriate, options for managing their disease when they are in remission, including both no treatment and treatment. The discussion should include the risk of

\textsuperscript{11} At the time of publication of this Evidence Update, not all azathioprine products had UK marketing authorisation for this indication, please see the \textit{summary of product characteristics} for each drug formulation.

\textsuperscript{12} At the time of publication of this Evidence Update, mercaptopurine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
inflammatory exacerbations (with and without drug treatment) and the potential side effects of drug treatment. Record the person’s views in their notes.

The guideline also includes recommendations from NICE TA187 that treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again. See NICE TA187 for the full recommendations on infliximab and adalimumab in Crohn’s disease.

Panaccione et al. (2013) reported long-term results from the CHARM and ADHERE trials. The CHARM trial was a placebo-controlled RCT of adalimumab in people with moderate to severe active Crohn’s disease, lasting for 56 weeks. Participants had induction therapy with adalimumab (80 mg at week 0 and 40 mg at week 2) and at week 4 were randomised to 1 of 3 groups: weekly adalimumab 40 mg, 2-weekly adalimumab 40 mg, or placebo. If patients had no response or relapse after week 12, they could move to open-label adalimumab treatment.

ADHERE was an open-label study that participants could enter after completing the CHARM trial (whether or not they were in remission). Any participant on open-label adalimumab treatment in CHARM continued into ADHERE on that treatment. Patients on blinded treatment on entry to ADHERE were randomly assigned to adalimumab 40 mg weekly or 2-weekly. The studies ended in December 2008, so not all patients reached week 212 from the baseline for CHARM (the final assessment point). Almost half of participants had previous treatment with another TNF inhibitor. Of 778 people randomised in CHARM, 467 people entered ADHERE and 349 people finished ADHERE at week 212. Remission was defined as a CDAI score lower than 150.

Remission at week 212 was assessed for people who had a reduction in CDAI of at least 70 points at the end of CHARM (n=329). In this group, using hybrid non-responder imputation to account for missing data in a modified intention to treat analysis, 30% (99 of 329) were still in remission at week 212. Use of last observation carried forward to account for missing data or ‘as observed’ per protocol analysis both resulted in an increased response rate. In a second analysis of only the 145 people who were in clinical remission at week 56 of CHARM, 54% (n=78) were still in remission at week 212.

In the 854 people who received any dose of adalimumab, 9736 adverse events occurred, 730 of which were classed as severe. Drug treatment was stopped in 252 people after an adverse event (30%). The most common category of adverse events was infection, with 1966 events, 102 of which were classed as severe. Tuberculosis was recorded in 3 people.

A limitation of the study was that analyses were complicated by the study stopping before all participants had completed 212 weeks of adalimumab treatment. The absence of a placebo group in the ADHERE portion of the studies means that conclusions cannot be drawn about remission in people continuing adalimumab treatment compared with those who stopped treatment after 1 year.

This evidence suggests that on continuing adalimumab treatment for 4 years, less than a third of people maintain remission; the same proportion of people may stop treatment because of adverse events. This evidence is unlikely to affect NICE CG152, although it may help to inform clinicians in their discussions with patients of the risks and benefits of continuing treatment when in remission.
1.4 Maintaining remission in Crohn’s disease after surgery

Maintenance treatment

NICE CG152 recommends offering azathioprine or mercaptopurine\(^{13}\) to maintain remission after surgery in people with adverse prognostic factors such as:

- more than one resection, or
- previously complicated or debilitating disease (for example, abscess, involvement of adjacent structures, fistulising or penetrating disease).

5-ASA\(^{14}\) treatment may also be considered to maintain remission after surgery.

Savarino et al. (2013) conducted an RCT in people undergoing surgical resection of ileal or ileocolonic Crohn’s disease to assess drug treatments in preventing relapse over 2 years. Within 4 weeks of surgery, patients at a single centre in Italy were randomly assigned by computer to 1 of 3 groups: adalimumab 40 mg/kg every 2 weeks (n=16); azathioprine 2 mg/kg daily (n=17); or mesalazine 3 g daily (n=18). People were excluded from the study if they needed a first surgery for a short fibrostenotic stricture after more than 10 years’ history of Crohn’s disease, if macroscopically active Crohn’s disease was noted but not resected during surgery, and if they had a stoma.

Antibiotics and immunomodulators were stopped 12 weeks before surgery, and continuous use of non-steroidal anti-inflammatory drugs was not allowed during the study. The primary outcome was the proportion of patients with clinical and endoscopic recurrence at 2 years. Clinical recurrence was defined as symptoms classed as mild or worse. Endoscopic recurrence was defined as more than 5 aphthous lesions or worse. Endoscopy results were available for 46 participants at 2 years, but earlier endoscopy results were used for 5 people who withdrew from the study.

Clinical recurrence occurred in 2 of 16 people (13%) in the adalimumab group compared with 11 of 17 people (65%) in the azathioprine group (OR=0.078, 95% CI 0.013 to 0.464), and with 9 of 18 people (50%) in the mesalazine group (OR=0.143, 95% CI 0.025 to 0.8169). Recurrence defined as CDAI score of more than 200 occurred in 1 of 16 (6%), 12 of 17 (71%), and 9 of 18 (50%) of participants respectively. The azathioprine and mesalazine groups did not differ significantly from each other for clinical recurrence or relapse measured by CDAI score.

In the adalimumab group, 1 patient discontinued because atopic dermatitis. In the azathioprine group, 1 patient withdrew because of a severe exacerbation of Crohn’s disease and 1 withdrew because of abdominal pain with increased pancreatic enzymes. In the mesalazine group, 2 patients withdrew because of severe exacerbations of Crohn’s disease. In total, 11 adverse events were reported in the adalimumab group, 15 in the azathioprine group, and 16 in the mesalazine group.

\(^{13}\) At the time of publication of this Evidence Update, mercaptopurine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

\(^{14}\) At the time of publication of this Evidence Update, mesalazine, olsalazine and balsalazide did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
The authors discussed the limitations of their study, which were: the lack of a placebo group; the inclusion of people who previously had treatment with immunomodulators or infliximab; and the small size of the study. The results of this study add to those of a previous RCT \((n=24)\) of infliximab for prevention of recurrence 1 year after surgery \((\text{Regueiro et al., 2009})\). In Regueiro et al. (2009), infliximab was significantly better than placebo for endoscopic recurrence \((p=0.0006)\) and histological recurrence \((p=0.01)\), but not for clinical remission \((p=0.38)\). Larger trials are needed to assess the use of TNF inhibitors in preventing recurrence of Crohn’s disease after surgery.

This trial suggests that adalimumab may be more effective than azathioprine or mesalazine in maintaining remission of Crohn’s disease after surgery. The evidence may have a potential impact on NICE CG152, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

**Key reference**

**Supporting reference**

### 1.5 Surgery

No new key evidence for this section was selected for inclusion in this Evidence Update.

### 1.6 Monitoring for osteopenia and assessing fracture risk

**Risk factors for osteoporosis**

NICE CG152 recommends referring to NICE clinical guideline 146 (NICE CG146) for recommendations on assessing the risk of fragility fracture in adults, noting that Crohn’s disease is a cause of secondary osteoporosis. Additional risk factors for osteoporosis relevant to people with Crohn’s disease include current or frequent reuse of oral or systemic glucocorticoids and low BMI (less than 18.5 kg/m²). Assessment of fracture risk should be considered in the presence of risk factors. See NICE CG146 for the full recommendation on targeting risk assessment for fragility fractures.

Atreja et al. (2012) conducted a retrospective study in adults with Crohn’s disease (64%) or ulcerative colitis (34%) attending a single centre in the USA for treatment of inflammatory bowel disease. Information on demographic, laboratory and dual-energy X-ray absorptiometry (DXA) scans was obtained from the institution’s clinical database and patient’s records were reviewed for risk factors for osteoporosis.

Risk factors assessed were categorised as ‘conventional’ (age, steroid use, menopausal status, and steroid use of more than 3 months) and ‘non-conventional’ (BMI of 21 mg/kg² or less, and total or subtotal colectomy). Osteopenia was defined as a T score between −1 and −2.5 standard deviations difference from the young adult mean. Osteoporosis was defined as −2.5 standard deviations difference from the young adult mean or greater.

DXA scan reports were available for 291 people with inflammatory bowel disease; 196 people had ‘conventional’ risk factors for osteoporosis and 95 had no ‘conventional’ risk factors. In the group with ‘conventional’ risk factors, osteoporosis was detected in 45 people (23%) and osteopenia in 94 people (48%). In those with no ‘conventional’ risk factors, osteoporosis was detected in 12 people (13%) and osteopenia in 39 people (41%).

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In multivariate logistic regression analysis, low BMI was a significant independent risk factor for osteoporosis (odds ratio [OR]=3.07, 95% CI 1.47 to 6.42, p=0.003). The significance of age (OR=1.02, 95% CI 1.00 to 1.05, p=0.05) and female gender (OR=2.09, 95% CI 0.99 to 4.4, p=0.05) was marginal. Steroid use and colectomy were not significantly associated with osteoporosis.

This study was conducted in the USA, where current guidelines about osteoporosis do not take low BMI into account; however, NICE guidance on assessing the risk of fragility fracture (NICE CG146) does include low BMI as a risk factor. The BMI threshold of less than 21 kg/m² as a risk factor for osteoporosis by Atreja et al. (2012) is not consistent with NICE’s definition of low body weight, which is BMI less than 18.5 kg/m². Additional limitations of the study include the potential for selection bias in that people referred to the study centre who had DXA scans may have had more severe disease and been more likely to have low body weight or osteoporosis.

This study suggests that low BMI may be the most important risk factor for osteoporosis in people with Crohn’s disease. This evidence is broadly consistent with current guidance in NICE CG152 and NICE CG146.

Key reference


1.7 Conception and pregnancy

NICE CG152 recommends giving information about the possible effects of Crohn's disease on pregnancy, including the potential risks and benefits of medical treatment and the possible effects of Crohn's disease on fertility. The summary of product characteristics for infliximab and adalimumab note that administration of live vaccines to infants exposed to these drugs in utero is not recommended for 5–6 months following the mother's last infusion during pregnancy.

Birth outcomes after TNF inhibitor treatment

Nielsen et al. (2013) conducted a systematic review to investigate birth outcomes in women with inflammatory bowel disease exposed to TNF inhibitors during pregnancy or up to 90 days before conception (n≥1533). An included study that assessed diseases other than inflammatory bowel disease did not report populations separately and the systematic review did not report separate outcomes for women with Crohn's disease or ulcerative colitis. Outcomes of interest were miscarriage, preterm delivery, stillbirth, low birth weight, congenital malformation, and infections in babies. Meta-analysis was not possible because of differences in study designs, selection of controls and outcomes measured.

Infliximab was the most studied TNF inhibitor with a total of 43 case-controlled studies, case series and case reports. The occurrence of complications was ‘limited’, even for exposure throughout pregnancy including the final trimester. However, fetal intra-uterine exposure to infliximab was up to 3 times higher than the levels in maternal peripheral blood. Adalimumab was studied in a total of 22 case reports, case series or case-controlled studies, with no increased risk of adverse pregnancy outcomes reported. Adalimumab was also transferred across the placenta in the third trimester. Although infections were not specifically reported, concerns about the effects of TNF inhibitors on the infant’s immune system remain.
The review had limitations resulting from the characteristics of the studies available for inclusion. Many studies did not fully report the total number of women exposed to treatment, disease activity, comorbidities, or whether participants were on multiple drug treatments, so establishing the cause of any harmful outcomes was difficult. No randomised controlled trials were identified in searches.

This evidence suggests that TNF inhibitors do not seem to be associated with major adverse effects when used during pregnancy, but infants exposed to these drugs in utero may be at increased risk of adverse reactions to live vaccines. This evidence adds to clinicians’ awareness of the risks and benefits of TNF inhibitors in pregnancy, but is unlikely to affect NICE CG152.

Key reference

Birth outcomes after thiopurine treatment

Akbari et al. (2013) conducted a systematic review and meta-analysis to investigate whether thiopurine treatment in women (or men) before conception and during pregnancy is associated with adverse birth outcomes. Studies were included if participants had a diagnosis of inflammatory bowel disease, ulcerative colitis or Crohn’s disease and had exposure to azathioprine or mercaptopurine within 3 months of conception or any time during pregnancy. Studies needed a comparator group unexposed to thiopurines and to report low birth weight, preterm birth or congenital malformation. All 8 studies identified were observational; in 7 the study design was retrospective for and 1 study was prospective.

In the 5 studies in women (n=3045), 4 were in a mixed Crohn’s disease and ulcerative colitis population and 1 study population had Crohn’s disease only. Admission to hospital was used as a surrogate marker for disease activity in 2 studies. Thiopurine use in women was not significantly associated with low birth weight (OR=1.01, 95% CI 0.96 to 1.06, p=0.831) or congenital malformations (OR=1.45, 95% CI 0.99 to 2.13, p=0.055). However, thiopurine use was significantly associated with preterm birth, defined as gestational age less than 37 weeks (OR=1.67, 95% CI 1.26 to 2.20, p<0.001). Sensitivity analyses showed no single study was driving the results, and the significance of findings did not change for any outcome when only the 3 largest studies were analysed.

In 3 studies in men (n=217) with Crohn’s disease or ulcerative colitis, 1 excluded men whose female partners received immunomodulator treatment, and 1 reported that female partners had no illnesses or exposure to toxins during pregnancy. No significant association between thiopurine use in men and congenital malformations was seen (OR=1.87, 95% CI 0.67 to 5.25, p=0.236).

No significant heterogeneity or evidence of publication bias was detected. Whether preterm birth was related to thiopurine use or to more severe disease activity making treatment necessary was unclear. Several included studies relied on self-report of thiopurine exposure and pregnancy outcomes. No study reported duration of treatment or daily dose used, so a possible dose-response relationship could not be assessed.

\[15\] At the time of publication of this Evidence Update, not all azathioprine products had UK marketing authorisation for this indication, please see the summary of product characteristics for each drug formulation.

\[16\] At the time of publication of this Evidence Update, mercaptopurine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
This study suggests that thiopurine use in pregnancy may be associated with preterm birth, but may not be associated with low birth weight or congenital malformations. This evidence adds to clinicians’ awareness of the risks and benefits of TNF inhibitors in pregnancy but no impact on NICE CG152 is expected.

Key reference

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Inducing remission in Crohn’s disease
- Adalimumab efficacy and safety for fistulizing Crohn’s disease after infliximab treatment failure

Maintaining remission in Crohn’s disease
- Safety of adalimumab treatment for up to 4 years, for remission of Crohn’s disease

Conception and pregnancy
- Thiopurines for IBD in female and male patients and pregnancy outcomes

Further evidence uncertainties for Crohn’s disease can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope
The scope of this Evidence Update is taken from the scope of the reference guidance:

- Crohn's disease. NICE clinical guideline 152 (2012)

Searches
The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 13 March 2012 (the end of the search period of NICE clinical guideline 152) to 16 April 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)

The Evidence Update search strategy replicates the strategy used by NICE CG152 (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/methodology/filters.html.

The searches for patient information and support also included a patient information filter, as per the reference guideline, with no restriction on study types.

Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.
Table 1 MEDLINE search strategy (adapted for individual databases)

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<th>MEDLINE search strategy (adapted for individual databases)</th>
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<tbody>
<tr>
<td>1</td>
<td>Crohn Disease/</td>
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<tr>
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<td>((crohn or crohn's or crohns) adj2 (disease or colitis)).ti,ab,hw.</td>
</tr>
<tr>
<td>3</td>
<td>((ileitis or enteritis) adj2 (terminal or regional)).ti,ab,hw.</td>
</tr>
<tr>
<td>4</td>
<td>((colitis or enteritis) adj2 granuloma*).ti,ab,hw.</td>
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<td>5</td>
<td>ileocoli*.ti,ab,hw.</td>
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<td>6</td>
<td>(epithelioid adj2 granuloma*).ti,ab,hw.</td>
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<tr>
<td>7</td>
<td>exp Inflammatory Bowel Diseases/</td>
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<td>8</td>
<td>(inflamm* adj2 bowel).ti,ab,hw.</td>
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<td>9</td>
<td>1 or 2 or 3 or 4 or 5 or 6 or 7 or 8</td>
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Figure 1 Flow chart of the evidence selection process

3197 records identified through search → 458 duplicates from searching

2739 records after duplicates removed → 1285 records excluded at first sift

1454 records included after first sift → 1334 records excluded at second sift

120 records included after second sift → 81 records excluded at critical appraisal and evidence prioritisation

39 records discussed by EUAG → 0 additional records identified by EUAG outside original search

14 records included by EUAG in published Evidence Update → 25 records excluded by EUAG

EUAG – Evidence Update Advisory Group
Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

**Professor John Mayberry – Chair**
Consultant Physician and Honorary Professor, University Hospitals of Leicester NHS Trust

**Ms Mary Brennan**
Clinical Nurse Specialist Paediatric Gastroenterology, Addenbrookes Hospital, Cambridge University Hospitals NHS Foundation Trust

**Ms Sarah Cripps**
Consultant Pharmacist – Gastroenterology, Oxford University Hospitals NHS Trust

**Dr Trevor Jones**
General Practitioner, St Johns House Medical Centre, Worcester

**Professor Alan Lobo**
Consultant Gastroenterologist, Sheffield Teaching Hospitals NHS Foundation Trust

**Professor John Nicholls**
Emeritus Consultant Surgeon, St Mark’s Hospital and Professor of Colorectal Surgery, Imperial College, London

**Dr Adrian Thomas**
Consultant Paediatric Gastroenterologist, Royal Manchester Children’s Hospital

Evidence Update project team

**Marion Spring**
Associate Director

**Dr Chris Alcock**
Clinical Lead – NICE Evidence Services

**Dr Chris Weiner**
Consultant Clinical and Public Health Adviser

**Cath White**
Programme Manager

**Swapna Mistry**
Project Manager