

# National Institute for Health and Care Excellence

4-year surveillance (2017) – [Crohn's disease: management](#) (2012)  
NICE guideline CG152

## Appendix A.1: Summary of new evidence from surveillance

### Patient information and support

**152–01    What are the primary information needs of adults with Crohn's disease in the UK?**

#### Recommendations derived from this question

- 1.1.1    Ensure that information and advice about Crohn's disease:
  - is age appropriate
  - is of the appropriate cognitive and literacy level, and
  - meets the cultural and linguistic needs of the local community. [2012]
- 1.1.2    Discuss treatment options and monitoring with the person with Crohn's disease, and/or their parent or carer if appropriate, and within the multidisciplinary team. Apply the principles outlined in patient experience in adult NHS services (NICE guideline CG138). [2012]
- 1.1.3    Discuss 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. [2012]
- 1.1.4    Give all people with Crohn's disease, and/or their parents or carers if appropriate, information, advice and support in line with published NICE guidance on:
  - smoking cessation
  - patient experience
  - medicines adherence
  - fertility. [2012]
- 1.1.5    Give people with Crohn's disease, and/or their parents or carers if appropriate, additional information on the following when appropriate:
  - possible delay of growth and puberty in children and young people
  - diet and nutrition
  - fertility and sexual relationships
  - prognosis
  - side effects of their treatment
  - cancer risk
  - surgery
  - care of young people in transition between paediatric and adult services
  - contact details for support groups. [2012]
- 1.1.6    Offer adults, children and young people, and/or their parents or carers, age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education. [2012]

## Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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### 152–02 What are the primary information needs of children and young people with Crohn's disease in the UK?

## Recommendations derived from this question

- 1.1.6 Offer adults, children and young people, and/or their parents or carers, age-appropriate multidisciplinary support to deal with any concerns about the disease and its treatment, including concerns about body image, living with a chronic illness, and attending school and higher education. [2012]

## Surveillance decision

This review question should not be updated.

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### 2-year surveillance summary

One US-based qualitative study<sup>1</sup> explored views of parents (n=35) of children with Crohn's disease (n=15) or juvenile idiopathic arthritis (n=20) who had considered treatment with TNF inhibitors. This study suggested that parents of children with Crohn's disease needed information to help decide whether to start TNF inhibitor treatments. Parents had particular worries about the risk of cancer and lack of long-term safety data.

### 4-year surveillance summary

No relevant evidence was identified.

### Topic expert feedback

No topic expert feedback was relevant to this evidence.

### Impact statement

The study identified in the 2-year surveillance review suggested that TNF inhibitors did not seem to be associated with major adverse effects when used during pregnancy. The evidence was considered to add to clinicians' awareness of the risks and benefits of TNF inhibitors in pregnancy, but was unlikely to affect recommendations in NICE CG152.

No studies were identified during the 4-year surveillance review. Furthermore, no topic expert feedback, related to this clinical question, was received.

New evidence is unlikely to change guideline recommendations.

## Inducing remission in Crohn's disease

### **152–03 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for induction of remission**

- compared with placebo?
- compared with 5-aminosalicylate (5-ASA) treatment?
- plus 5-ASA treatment compared with placebo?
- compared with azathioprine or mercaptopurine (AZA/MP)?
- plus azathioprine or mercaptopurine (AZA/MP) compared with conventional glucocorticosteroid treatment plus placebo?
- compared with methotrexate?
- plus methotrexate compared with conventional glucocorticosteroid treatment plus placebo?

### **Recommendations derived from this question**

#### *Monotherapy*

- 1.2.1 Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. [2012].
- 1.2.3 In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects. [2012]
- 1.2.4 In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]
- 1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. [2012]
- 1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

#### *Add-on treatment*

- 1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide 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. [2012]
- 1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). [2012]
- 1.2.9 Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:

- there are two or more inflammatory exacerbations in a 12-month period, or
  - the glucocorticosteroid dose cannot be tapered. [2012]
- 1.2.10 Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the current online version of the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity. [2012]
- 1.2.11 Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate. [2012]

## Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

**152–04 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for induction of remission compared with**

- placebo?
- conventional glucocorticosteroid treatment?
- 5-aminosalicylate (5-ASA) treatment?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

## Recommendations derived from this question

### *Monotherapy*

- 1.2.1 Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. [2012].
- 1.2.3 In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects. [2012]
- 1.2.4 In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]
- 1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. [2012]
- 1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

### Add-on treatment

- 1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide 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. [2012]
- 1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). [2012]
- 1.2.9 Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:
- there are two or more inflammatory exacerbations in a 12-month period, or
  - the glucocorticosteroid dose cannot be tapered. [2012]
- 1.2.10 Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the current online version of the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity. [2012]
- 1.2.11 Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate. [2012]

### Surveillance decision

This review question should not be updated.

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#### 2-year surveillance summary

No relevant evidence was identified.

#### 4-year surveillance summary

A network meta-analysis<sup>2</sup> which compared the efficacy of budesonide and mesalazine for treating Crohn's disease, showed Budesonide 9 mg/day, or at higher doses (15 or 18 mg/day), was significantly better at inducing and maintaining remission than placebo. Authors stated that no other comparisons (i.e. different doses of mesalazine versus placebo or budesonide) were statistically significant. No significant difference in adverse event rates was observed between budesonide, mesalazine and placebo.

One systematic review<sup>3</sup> aimed to assess the safety and efficacy of oral budesonide for induction of remission of Crohn's disease. Pooled analysis of 3 studies indicated that budesonide 9 mg was found to be significantly more effective than placebo for induction of clinical remission at 8 week follow-up.

Compared to conventional corticosteroids, budesonide was significantly less effective at inducing remission of Crohn's disease in all patients as well as a subgroup of patients with severe disease. Significant heterogeneity precluded pooled analysis of studies comparing budesonide and mesalazine. One of the identified studies indicated that budesonide was significantly superior to mesalazine at 8 week follow-up, whereas the other study indicated no difference between treatments. The adverse event rate was significantly lower in patients treated by budesonide than those treated by conventional steroids. Finally, authors reported budesonide was significantly better at preserving adrenal function than conventional steroids.

In an RCT<sup>4</sup> of patients with mild-to-moderate active Crohn's disease treated by once-daily or three times daily oral budesonide, authors reported that once-daily therapy was non-inferior to three times daily therapy for induction of remission. The mean time to remission was

21.9 days in the once-daily group and 21.4 days in the three times daily group. In a subgroup analysis of patients with baseline Simplified Endoscopic Activity Score for Crohn's Disease scale ulcer score greater than 1, complete mucosal healing occurred in 32.8% of patients in the once-daily group and 41.4% in the three times daily group. Furthermore, deep remission (mucosal healing and clinical remission) was observed in 26.6% of patients in the once-daily group and 32.8% of patients in the three times daily group. Similar rates of treatment-emergent adverse events were reported in each group.

#### Topic expert feedback

No topic expert feedback was relevant to this evidence.

#### Impact statement

No studies were identified during the 2-year surveillance review. One systematic review was identified during the 4-year surveillance review which reported that budesonide was significantly less effective at inducing remission of Crohn's than conventional glucocorticosteroids. Furthermore, 1 systematic review reported that adverse event rates were

significantly lower in patients treated by budesonide than those treated by conventional steroids. This is in line with guideline recommendations which state that clinicians should explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects.

A network meta-analysis indicated no significant difference between budesonide and mesalazine. Conversely, 1 RCT, identified in a systematic review, reported that budesonide was superior to mesalazine for induction of remission of Crohn's disease. CG152 recommends that clinicians should explain that 5-aminosalicylates are less effective than conventional glucocorticosteroids or budesonide but may have fewer side effects than conventional glucocorticosteroids.

Overall, the identified new evidence was insufficient to trigger an update of this clinical question.

New evidence is unlikely to change guideline recommendations.

### 152–05 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for induction of remission compared with

- placebo?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

### Recommendations derived from this question

#### Monotherapy

- 1.2.1 Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. [2012].
- 1.2.3 In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects. [2012]
- 1.2.4 In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective

than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]

1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. [2012]

1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

### *Add-on treatment*

1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide 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. [2012]

1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). [2012]

1.2.9 Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:

- there are two or more inflammatory exacerbations in a 12-month period, or
- the glucocorticosteroid dose cannot be tapered. [2012]

1.2.10 Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the current online version of the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity. [2012]

1.2.11 Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate. [2012]

### **Surveillance decision**

This review question should not be updated.

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#### **2-year surveillance summary**

No relevant evidence was identified.

#### **4-year surveillance summary**

One systematic review<sup>5</sup> of 20 RCTs aimed to assess the safety and efficacy of 5-aminosalicylates for induction of remission or clinical response of Crohn's disease. Studies comparing 5-aminosalicylates with placebo, corticosteroids or other aminosalicylates were included. Pooled analysis of 2 studies showed no significant difference in induction of remission rates between patients treated by sulfasalazine and those who received placebo at 18 week follow-up. Pooled analysis of 2 studies indicated that treatment with sulfasalazine resulted in significantly lower remission rates compared with corticosteroid

monotherapy or sulfasalazine plus corticosteroid combination therapy. One study reported that olsalazine was significantly less effective than placebo for induction of remission. Furthermore, another study reported no significant difference in remission rates between patients treated by low-dose mesalazine and those who received placebo at 6 week follow-up. Pooled analysis of 3 studies revealed no significant difference in clinical remission rates between high dose controlled-release mesalazine and placebo. One study reported that high dose controlled-release mesalazine was significantly less effective at inducing remission than budesonide. Results from another study revealed no significant difference in remission rates in patients treated by high dose delayed-release mesalazine and



those who received placebo. Furthermore, no significant differences in remission rates were observed in comparisons between high dose delayed-release mesalazine and conventional corticosteroids as well as comparisons between high dose delayed-release mesalazine and budesonide. In relation to adverse events no significant differences in adverse event or serious adverse event rates were observed in the following comparisons: sulfasalazine versus placebo, sulfasalazine versus corticosteroids, and low dose mesalazine versus placebo. Furthermore, no significant difference in withdrawal due to adverse event rates were observed between groups in studies which compared sulfasalazine with corticosteroids, and mesalazine with placebo. Adverse events that were commonly reported included headache, nausea, vomiting, abdominal pain and diarrhoea.

In 1 systematic review<sup>6</sup> of 7 RCTs, investigators identified 1 study which reported that methotrexate significantly improved induction of remission rates compared to 5-aminosalicylates.

#### Topic expert feedback

No topic expert feedback was relevant to this evidence.

#### Impact statement

In 1 systematic review pooled analysis of 2 studies indicated that treatment with sulfasalazine resulted in significantly lower remission rates compared with corticosteroid monotherapy or sulfasalazine plus corticosteroid combination therapy. This was

mainly in line with guideline recommendations. In the same systematic review pooled analysis of 3 studies indicated no significant differences in induction of remission rates between mesalazine and placebo. Additionally, 1 identified study reported that mesalazine was inferior to budesonide whereas another study reported no significant difference between high-dose mesalazine and budesonide. These findings were in line with guideline recommendations. CG152 recommends that 5-aminosalicylates should be offered to patients who cannot tolerate or in whom glucocorticosteroid treatment is contraindicated. Furthermore, the guideline states that clinicians should explain that 5-aminosalicylates are less effective than conventional glucocorticosteroids or budesonide but may have fewer side effects than conventional glucocorticosteroids.

In another systematic review, authors reported that 5-aminosalicylates significantly improved induction of remission rates compared to methotrexate. This is in line with guideline recommendations which state that azathioprine, mercaptopurine or methotrexate monotherapy should not be used to induce remission.

Topic experts did not provide any feedback related to this clinical question. Overall, it was considered that the identified new evidence was in line with guideline recommendations.

New evidence is unlikely to change guideline recommendations.

### 152–06 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for induction of remission compared with

- placebo?
- methotrexate?

#### Subquestion

– In individuals diagnosed with Crohn's disease what is the incidence of serious adverse events for the following subgroups:

- individuals with normal blood TPMT activity, on a standard dose of azathioprine
- individuals with low blood TPMT activity, on a low dose of azathioprine



- individuals whose blood TPMT is unknown, on a standard dose of azathioprine?

## Recommendations derived from this question

### *Monotherapy*

- 1.2.1 Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. [2012].
- 1.2.3 In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects. [2012]
- 1.2.4 In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]
- 1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. [2012]
- 1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

### *Add-on treatment*

- 1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide 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. [2012]
- 1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). [2012]
- 1.2.9 Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:
  - there are two or more inflammatory exacerbations in a 12-month period, or
  - the glucocorticosteroid dose cannot be tapered. [2012]
- 1.2.10 Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the current online version of the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity. [2012]
- 1.2.11 Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate. [2012]

## Surveillance decision

This review question should not be updated.

## 2-year surveillance summary

Searches identified a Cochrane review<sup>7</sup> 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. There was no significant difference between azathioprine or mercaptopurine (48%) and placebo (37%) for the remission of Crohn's disease (risk ratio [RR], 1.23; 5 studies, n=380).

One randomised controlled trial<sup>8</sup> (n=126) 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. No significant differences were seen in time to treatment failure between groups (hazard ratio [HR], 1.16).

## 4-year surveillance summary

In 1 systematic review<sup>6</sup> investigators identified 2 studies which reported no significant differences in remission rates between patients treated by 6-mercaptopurine and those treated by low dose oral methotrexate. Another identified study reported no significant difference in remission rates between azathioprine and methotrexate therapies. Results from 1 of the identified studies indicated that adverse event rates were significantly lower in patients treated by azathioprine compared with those treated by methotrexate.

In an RCT<sup>9</sup> of 50 patients with Crohn's disease treated by standard dose (2 mg/kg/day) or low dose (1 mg/kg/day) azathioprine clinical remission and clinical response rates were significantly higher in the standard dose group at 48 week follow-up. The recurrence rate was significantly higher in the low-dose azathioprine group. In relation to adverse events, authors stated that 1 patient had arthritis and 2 patients had myelosuppression in the both study arms. One patient had pancreatitis in the low-dose group.

One RCT<sup>10</sup> assessed whether azathioprine therapy for inducing remission of Crohn's disease was optimised by individualised dosing based on thiopurine methyltransferase activity and 6-thioguanine nucleotides (6TGN) concentrations. Patients (n=50) with Crohn's disease were randomised to weight-based or

individualised azathioprine dosing. No significant difference in clinical remission rates were observed between the individualised dosing group and the weight-based dosing group at 16-week follow-up. Authors reported that there was no significant difference in median 6TGN concentrations between remitters and non-remitters at 16 week follow-up

## Topic expert feedback

One topic expert suggested that the efficacy of azathioprine can be increased with the use of allopurinol (an orally administered xanthine oxidase inhibitor). They suggested that this offers an additional step before changing treatment to methotrexate. Another topic expert suggested that the use of allopurinol avoids escalation to azathioprine treatment, resulting in considerable cost savings. One topic expert suggested that 6-thioguanine measurements were useful before changing azathioprine treatment to ensure that adequate doses are being used. No studies were suggested by topic experts.

## Impact statement

During the 2-year surveillance review, findings on azathioprine and mercaptopurine monotherapy were considered to be consistent with NICE CG152.

The systematic review identified in the 4-year surveillance review indicated no differences in remission rates between patients treated by azathioprine or 6-mercaptopurine and those treated by methotrexate. Furthermore, the study indicated that thiopurine therapy was associated with fewer adverse events than methotrexate therapy. The evidence from the systematic review is unlikely to affect guideline recommendations as methotrexate is recommended when people cannot tolerate azathioprine or mercaptopurine.

One RCT identified during the 4-year surveillance review compared different doses of azathioprine and was considered to have little impact on recommendations as the recommendations do not state the dose of the medication.

One topic expert suggested that 6-thioguanine measurements were useful before changing azathioprine treatment to ensure that adequate doses are being used. This was supported by results from 1 RCT of 50 patients which assessed individualised dosing based on thiopurine methyltransferase activity and 6-

thioguanine nucleotides concentrations. The small sample size of this study meant that there was insufficient evidence to prompt an update of the guideline. As a result, more research on the potential benefits of measuring 6-thioguanine concentrations is needed to confirm its usefulness in monitoring

azathioprine dosage suitability in patients with Crohn's disease.

New evidence is unlikely to change guideline recommendations.

#### **152–07 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for induction of remission**

- **compared with placebo?**
- **plus conventional glucocorticosteroid treatment compared with placebo plus conventional glucocorticosteroid treatment?**

#### **Recommendations derived from this question**

##### *Monotherapy*

- 1.2.1 Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. [2012].
- 1.2.3 In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that budesonide is less effective than a conventional glucocorticosteroid but may have fewer side effects. [2012]
- 1.2.4 In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. Explain that 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side effects than a conventional glucocorticosteroid. [2012]
- 1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. [2012]
- 1.2.6 Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. [2012]

##### *Add-on treatment*

- 1.2.7 Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide 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. [2012]
- 1.2.8 Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). [2012]
- 1.2.9 Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:
  - there are two or more inflammatory exacerbations in a 12-month period, or

- the glucocorticosteroid dose cannot be tapered. [2012]
- 1.2.10 Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the current online version of the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity. [2012]
- 1.2.11 Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate. [2012]

## Surveillance decision

This review question should not be updated.

### 2-year surveillance summary

A Cochrane review<sup>11</sup> pooled data from 7 randomised controlled trials (RCTs; n=495) comparing methotrexate with placebo or active control for remission of Crohn's disease. 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). 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).

### 4-year surveillance summary

In 1 systematic review<sup>6</sup> investigators identified 2 studies which reported no significant differences in remission rates between patients treated by low dose oral methotrexate (15 mg or 12.5 mg per week) and those who received placebo. One identified study reported that high dose intramuscular methotrexate was significantly superior at inducing remission than placebo. In 1 study, rates of withdrawal due to adverse events were significantly higher in patients treated by methotrexate compared to those who received placebo. Common adverse

events included nausea and vomiting, abdominal pain, diarrhoea, skin rash and headache. The review did not perform any pooled analysis due to heterogeneity between identified studies.

### Topic expert feedback

No topic expert feedback was relevant to this evidence.

### Impact statement

The identified studies in the 2-year surveillance review suggested that methotrexate may not be effective for inducing remission in Crohn's disease. This evidence was considered unlikely to have an impact on NICE CG152. The systematic review identified during the 4-year surveillance review did not perform any pooled analysis due to heterogeneity between identified studies. One study included in the systematic review reported no significant differences between methotrexate and placebo. The other study included in the systematic review assessed safety outcomes as opposed to induction of remission. More research is needed to clarify the role of methotrexate for induction of remission of Crohn's disease.

New evidence is unlikely to change guideline recommendations.

**152–08 In adults and children diagnosed with Crohn’s disease what is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) as a sole source of nutrition for induction of remission compared with**

- usual diet?
- conventional glucocorticosteroid treatment?
- budesonide?
- a combination of conventional glucocorticosteroid treatment plus 5-ASA treatment?
- a combination of conventional glucocorticosteroid treatment plus azathioprine or mercaptopurine?
- a combination of conventional glucocorticosteroid treatment plus methotrexate methotrexate?

## Recommendations derived from this question

### *Monotherapy*

1.2.2 Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:

- children in whom there is concern about growth or side effects, and
- young people in whom there is concern about growth. [2012]

## Surveillance decision

This review question should not be updated.

### 2-year surveillance summary

No relevant evidence was identified.

### 4-year surveillance summary

One RCT<sup>12</sup> aimed to assess the impact of a high-fibre diet on the quality of life of people diagnosed with Crohn’s disease. Results indicated that people who consumed whole wheat bran in their diet had significantly better quality of life and gastrointestinal function than those who did not. No significant difference in C-reactive protein or erythrocyte sedimentation rates were observed between groups.

### Topic expert feedback

No topic expert feedback was relevant to this evidence.

### Impact statement

No evidence was identified during the 2-year surveillance review. The RCT identified in the 4-year surveillance review did not report the impact of enteral nutrition on induction of remission, therefore the evidence does not affect guideline recommendations was identified.

New evidence is unlikely to change guideline recommendations.

**152–09 In adults and children diagnosed with Crohn’s disease what is the clinical and cost effectiveness for induction of remission of enteral nutrition (elemental, semi-elemental and polymeric) plus medical therapy versus usual diet?**

### Recommendations derived from this question

#### *Monotherapy*

1.2.2 Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:

- children in whom there is concern about growth or side effects, and
- young people in whom there is concern about growth. [2012]

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

**152–10 Infliximab and adalimumab (recommendations were taken from the Technology Appraisal on [infliximab and adalimumab for the treatment of Crohn's disease](#) TA187)**

### Recommendations derived from this question

#### *Infliximab and adalimumab*

- 1.2.12 Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see 1.2.18) 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 (see 1.2.16) to determine whether ongoing treatment is still clinically appropriate. [2012]
- 1.2.13 Treatment as described in 1.2.12 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. [2012]
- 1.2.15 Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab 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 (see 1.2.16) to determine whether ongoing treatment is still clinically appropriate. [2012]
- 1.2.16 Treatment with infliximab or adalimumab (see 1.2.12 and 1.2.15) 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. [2012]

- 1.2.17 Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months. [2012]
- 1.2.18 For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above. [2012]
- 1.2.19 When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate. [2012]
- 1.2.20 Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease. [2012]

## Surveillance decision

This review question should not be updated.

### 2-year surveillance summary

Three systematic reviews<sup>13-15</sup> were identified which assessed the safety or efficacy of anti-TNF therapy for induction of remission of Crohn's disease.

### 4-year surveillance summary

Literature searches yielded 3 network meta-analyses<sup>16-18</sup>, 9 systematic reviews<sup>19-27</sup>, 5 RCTs<sup>28-32</sup> and 3 health economic evaluations<sup>33-35</sup> which assessed the safety, efficacy or cost effectiveness of infliximab or adalimumab for the treatment of Crohn's. CG152 does not review the anti-tumour necrosis factor agents because guidance is available from the

technology appraisal on [Infliximab and adalimumab for the treatment of Crohn's disease](#) (TA187).

### Topic expert feedback

No topic expert feedback was received relating to CG152 recommendations.

### Impact statement

The NICE technology appraisal team has been informed about all new evidence.

New evidence is unlikely to change guideline recommendations.



**152–11 What is the clinical and cost-effectiveness of TNF alpha inhibitor monoclonal antibodies (infliximab and adalimumab) given in combination with immunosuppressants compared with infliximab or adalimumab alone for inducing remission in adults and children (6-17 years) with active Crohn's disease?**

**Recommendations derived from this question**

*Infliximab and adalimumab*

- 1.2.14 When a person with Crohn's disease is starting infliximab or adalimumab (in line with recommendations 1.2.12, 1.2.15, 1.2.17 and 1.2.20), discuss options of:
- monotherapy with one of these drugs or
  - combined therapy (either infliximab or adalimumab, combined with an immunosuppressant)
- and tell the person there is uncertainty about the comparative effectiveness and long-term adverse effects of monotherapy and combined therapy. [new 2016]

**Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.

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*Maintaining remission in Crohn's disease*

**152–12 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for maintenance of remission for 12 months or longer**

- compared with placebo?
- compared with methotrexate?
- ***plus* conventional glucocorticosteroid or 5-ASA treatment compared with placebo *plus* conventional glucocorticosteroid or 5-ASA treatment?**

**Recommendations derived from this question**

- 1.3.1 Discuss 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. Record the person's views in their notes. [2012]
- 1.3.2 Offer colonoscopic surveillance in line with colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE guideline CG118). [2012]

*Follow-up during remission for those who choose not to receive maintenance treatment*

- 1.3.3 When people choose not to receive maintenance treatment:
- discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see

- ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill-health)
- ensure they know how to access the healthcare system if they experience a relapse
- discuss the importance of not smoking. [2012]

#### *Maintenance treatment for those who choose this option*

- 1.3.4 Offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission. [2012]
- 1.3.5 Consider azathioprine or mercaptopurine to maintain remission in people who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations). [2012]

### **Surveillance decision**

This review question should not be updated.

#### **2-year surveillance summary**

##### *Adverse events associated with thiopurine treatment*

One retrospective study<sup>36</sup> investigated thiopurine toxicity using a Spanish national database containing information on thiopurine prescriptions from 1973 to 2010. 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%). 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.

##### *Maintenance treatment with adalimumab*

Literature searches identified long-term results<sup>37</sup> from the CHARM and ADHERE trials. 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.

#### **4-year surveillance summary**

One systematic review<sup>38</sup> pooled data from RCTs which compared the efficacy of oral azathioprine or 6-mercaptopurine with placebo or other active agents in patients with Crohn's disease in remission. Pooled analysis of 6 studies indicated that azathioprine was significantly better than placebo at maintaining remission between 6 and 18 month follow-up assessments. Pooled analysis of 2 studies indicated no significant difference in the number of patients treated by azathioprine or 6-mercaptopurine who remained in remission and the number of patients treated by mesalazine or sulfasalazine who remained in remission. In 1 study, authors reported that azathioprine was significantly superior to budesonide for maintenance of remission at 1 year follow-up. Another study reported no significant difference in remission rates between patients treated by azathioprine plus infliximab combination therapy and infliximab monotherapy at 1 year follow-up. One study reported no significant difference in maintenance of remission rates between patients treated by 6-mercaptopurine and those who received methotrexate. In another study, authors reported that early azathioprine therapy was significantly superior at maintaining remission than a conventional management strategy (no further details provided). Rates of adverse events, withdrawals due to adverse events and serious adverse events were significantly higher in patients treated by azathioprine compared those who received placebo. Furthermore, serious adverse event rates were significantly

higher in patients treated by azathioprine or 6-mercaptopurine compared to those treated by mesalazine or sulfasalazine. Common adverse events included pancreatitis, leukopenia, nausea, allergic reaction and infection.

In 1 systematic review<sup>39</sup>, pooled analysis of 2 RCTs revealed no significant difference in numbers of patients treated by 6-mercaptopurine who remained in remission and numbers of patients treated by methotrexate who remained in remission.

In 1 systematic review<sup>40</sup> investigators assessed discontinuation rates of patients who received various medications for maintenance of remission of Crohn's. The primary outcome measure of interest was the number needed to discontinue (NND) divided by the number needed to treat (NNT). Authors reported that azathioprine or 6-mercaptopurine were associated with more discontinuations than remission in maintenance trials (NND/NNT = 0.92). In relation to induction of remission, methotrexate was associated with similar rates of discontinuations and remission (NND/NNT = 1.4). Pooled analysis from which evaluated the efficacy of anti-TNF agent revealed an NND/NNT = 37.9. Authors reported that trials with anti-trafficking agents (not defined) had fewer discontinuations than placebo. No further details were provided.

One RCT<sup>41</sup> aimed to assess the effects of withdrawal of long-term azathioprine maintenance therapy in 52 patients with Crohn's disease. Patients with Crohn's disease who had received azathioprine maintenance therapy for more than 4 years were randomised to discontinue therapy or continue therapy. Authors stated that the trial was stopped early due to low recruitment rates. During the 2 year follow-up period clinical relapse was reported in 31% of patients who discontinued therapy and 15% of patients who continued therapy. The duration of time until clinical relapse was not significantly different between groups. Authors stated that life-table analysis revealed no significant difference in remission rates between groups.

#### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

#### **Impact statement**

The majority of evidence identified during the 2-year surveillance review was considered to be consistent with NICE CG152. One study

suggested 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. The evidence was considered to be consistent with NICE CG152, which recommends clinicians should discuss the potential side effects of drug maintenance treatment in people whose Crohn's disease is in remission. In another study, results indicated that upon continuing adalimumab treatment for 4 years, less than a third of people maintain remission. Additionally, the same proportion of people may stop treatment because of adverse events. Although the study could help inform clinicians in their discussions with patients about the risks and benefits of continuing treatment when in remission, it was considered that the study was unlikely to affect NICE CG152.

During the 4-year surveillance review, 1 systematic review was identified which compared the efficacy of oral azathioprine or 6-mercaptopurine with active therapy or placebo in patients with Crohn's disease in remission. However most analyses performed in the systematic review were based on only 1 or 2 studies. The systematic review indicated no significant differences between maintenance of remission rates of patients treated by thiopurines and those treated by mesalazine and reported that azathioprine was significantly superior to budesonide for maintenance of remission at 1 year follow-up. Currently CG152 makes no recommendations about the use of mesalazine as maintenance therapy. Furthermore, the clinical guideline recommends that conventional glucocorticosteroids or budesonide should not be offered to maintain remission. It was considered that more evidence was needed to establish the efficacy of immunomodulators compared to other medications.

One systematic review, identified during the 4-year surveillance review, reported no significant difference in maintenance of remission rates between 6-mercaptopurine and methotrexate therapy (based on data from 2 RCTs). The surveillance team considered that more evidence on safety and cost effectiveness was needed to ascertain whether methotrexate could be used as first-line therapy for maintaining remission of Crohn's. Two other studies assessed outcomes of patients with

Crohn's disease in remission who discontinued thiopurine therapy. It was considered that the study's findings were not sufficient to trigger an update of the guideline. Topic experts did not provide any feedback related to this clinical question.

Overall, it was considered that none of the identified studies contradicted guideline

recommendations that azathioprine or mercaptopurine monotherapy should be used to maintain remission of Crohn's disease.

New evidence is unlikely to change guideline recommendations.

**152–13 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for maintenance of remission for 12 months or longer**

- **compared with placebo?**
- **plus conventional glucocorticosteroid treatment compared with placebo plus conventional glucocorticosteroid treatment?**

**Recommendations derived from this question**

- 1.3.1 Discuss 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. Record the person's views in their notes. [2012]
- 1.3.2 Offer colonoscopic surveillance in line with colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE guideline CG118). [2012]

*Follow-up during remission for those who choose not to receive maintenance treatment*

- 1.3.3 When people choose not to receive maintenance treatment:
- discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see
  - ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill-health)
  - ensure they know how to access the healthcare system if they experience a relapse
  - discuss the importance of not smoking. [2012]

*Maintenance treatment for those who choose this option*

- 1.3.6 Consider methotrexate to maintain remission only in people who
- needed methotrexate to induce remission, or
  - have tried but did not tolerate azathioprine or mercaptopurine for maintenance or
  - have contraindications to azathioprine or mercaptopurine (for example, deficient TPMT activity or previous episodes of pancreatitis). [2012]

**Surveillance decision**

This review question should not be updated.

## 2-year surveillance summary

No relevant evidence was identified.

## 4-year surveillance summary

One systematic review<sup>39</sup> aimed to evaluate the safety and efficacy of methotrexate for maintenance of remission of Crohn's disease. RCTs that compared methotrexate to placebo or any other active intervention were included. Pooled analysis of indicated that intramuscular methotrexate was significantly superior to placebo for maintaining remission at 40 week follow-up. Conversely, no significant difference in the proportions of patients that remained in remission at 36 week follow-up, were observed between patients treated by methotrexate and those who received placebo. Authors noted that adverse events associated with methotrexate therapy were generally mild and resolved upon discontinuation or with folic acid supplementation. Common adverse events included nausea and vomiting, symptoms of a

cold, abdominal pain, headache, joint pain or arthralgia, and fatigue.

## Topic expert feedback

No topic expert feedback was relevant to this evidence.

## Impact statement

No studies were identified during the 2-year surveillance review. The 1 systematic review, identified during the 4-year surveillance review, compared methotrexate with placebo. None of the study's findings contradicted guideline recommendations which recommend the use of methotrexate in patients who fail to respond to, or are intolerant to thiopurine therapy. Furthermore, topic experts did not provide any feedback related to this clinical question.

New evidence is unlikely to change guideline recommendations.

## 152–14 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for maintenance of remission for 12 months or longer

- compared with placebo?
- compared with 5-aminosalicylate (5-ASA) treatment?
- plus 5-ASA treatment with conventional glucocorticosteroid plus placebo?
- compared with azathioprine or mercaptopurine (AZA/MP)?
- plus azathioprine or mercaptopurine compared with conventional glucocorticosteroid treatment plus placebo?
- compared with methotrexate?

## Recommendations derived from this question

- 1.3.1 Discuss 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. Record the person's views in their notes. [2012]
- 1.3.2 Offer colonoscopic surveillance in line with colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE guideline CG118). [2012]

## *Follow-up during remission for those who choose not to receive maintenance treatment*

- 1.3.3 When people choose not to receive maintenance treatment:
- discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see

- ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill-health)
- ensure they know how to access the healthcare system if they experience a relapse
- discuss the importance of not smoking. [2012]

#### *Maintenance treatment for those who choose this option*

1.3.7 Do not offer a conventional glucocorticosteroid or budesonide to maintain remission. [2012]

### **Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.

**152–15 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for maintenance of remission for 12 months or longer compared with**

- placebo?
- conventional glucocorticosteroid treatment?
- 5-aminosalicylate (5-ASA) treatment?
- azathioprine or mercaptopurine (AZA/MP)?
- methotrexate?

### **Recommendations derived from this question**

- 1.3.1 Discuss 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. Record the person's views in their notes. [2012]
- 1.3.2 Offer colonoscopic surveillance in line with colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE guideline CG118). [2012]

#### *Follow-up during remission for those who choose not to receive maintenance treatment*

- 1.3.3 When people choose not to receive maintenance treatment:
- discuss and agree with them, and/or their parents or carers if appropriate, plans for follow-up, including the frequency of follow-up and who they should see
  - ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (most frequently, unintended weight loss, abdominal pain, diarrhoea, general ill-health)
  - ensure they know how to access the healthcare system if they experience a relapse
  - discuss the importance of not smoking. [2012]

#### *Maintenance treatment for those who choose this option*

1.3.7 Do not offer a conventional glucocorticosteroid or budesonide to maintain remission. [2012]

## Surveillance decision

This review question should not be updated.

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### 2-year surveillance summary

No relevant evidence was identified.

### 4-year surveillance summary

One systematic review<sup>42</sup> of 12 RCTs aimed to evaluate the safety and efficacy of oral budesonide for maintaining remission of Crohn's disease. No significant differences in continued remission rates were observed between budesonide 6mg and placebo at 3, 6 and 12 month follow-up. No significant differences in continued remission rates were observed between budesonide 3mg and placebo at 6 and 12 month follow-up. In relation to comparisons with active agents, no significant differences in continued remission rates at 12 months were observed between budesonide and weaning doses of prednisolone. One identified study of 77 patients reported no significant difference in maintenance of remission rates between budesonide and azathioprine. Authors reported that budesonide was significantly better at maintaining remission than mesalazine 3g/day at 12 month follow-up. Budesonide 6 mg was associated with slight improvements in Crohn's disease activity index scores at 6 and 12 month follow-up assessments. The mean time to relapse was significantly shorter in patients treated by budesonide compared to those treated by azathioprine. No significant difference in adverse event rates were observed between patients treated by budesonide and those who received placebo. Commonly reported treatment-related adverse effects included acne, moon facies, hirsutism,

mood swings, insomnia, weight gain, striae, and hair loss.

### Topic expert feedback

No topic expert feedback was relevant to this evidence.

### Impact statement

No studies were identified during the 2-year surveillance review. During the 4-year surveillance review, 1 systematic review was identified which reported that no significant differences in maintenance of remission rates between budesonide and placebo at 12 month follow-up. The systematic review reported that budesonide was superior to mesalazine. Currently, CG152 does not make recommendations on mesalazine for maintaining remission of Crohn's disease. One of the identified studies reported no significant difference in maintenance of remission rates of patients treated by budesonide and those treated by azathioprine. However, it was noted that the study sample size was relatively small (n=77). As a result, it was considered that the study's findings were unlikely to affect guideline recommendations.

Topic experts did not provide any feedback related to this clinical question. As a result, it was considered that there was no new evidence that would affect guideline recommendations.

New evidence is unlikely to change guideline recommendations.



**152–16 In individuals diagnosed with Crohn’s disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for maintenance of remission compared with**

- **placebo?**
- **azathioprine or mercaptopurine (AZA/MP)?**
- **methotrexate?**

**Recommendations derived from this question**

Not linked to any guideline recommendations.

**Surveillance decision**

This review question should not be updated.

**2-year surveillance summary**

No relevant evidence was identified.

**4-year surveillance summary**

One systematic review<sup>43</sup> of 12 studies assessed the safety and efficacy of oral 5-aminosalicylic acid for maintenance of remission of Crohn’s disease. Investigators included RCTs which compared 5-aminosalicylates with either placebo or sulfasalazine. No studies comparing 5-aminosalicylates with sulfasalazine were identified. Pooled analysis of 11 studies indicated no significant difference in relapse rates of patients treated by 5-aminosalicylates and those who received placebo at 12 month follow-up. One identified study reported no significant difference between 5-aminosalicylates and placebo at 24 month follow-up. Another study, which focussed on children with Crohn’s disease, reported no significant difference in relapse rates between the 5-aminosalicylate group and the placebo group at 12 month follow-up. No significant differences in adverse event and serious adverse event rates were observed between groups. Furthermore, no significant differences in rates of withdrawal due to adverse events were observed between groups. Common adverse events reported in the studies included diarrhoea, nausea and vomiting, abdominal pain, headache and skin rash.

In 1 systematic review<sup>38</sup> pooled analysis of 2 studies indicated no significant difference in the number of patients treated by azathioprine or 6-mercaptopurine who remained in remission and

the number of patients treated by mesalazine or sulfasalazine who remained in remission.

In 1 systematic review<sup>39</sup>, an RCT was identified which reported no significant differences between 5-aminosalicylic acid and methotrexate for maintaining remission of Crohn’s disease.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

No studies were identified during the 2-year surveillance review. One systematic review, identified during the 4-year surveillance review, compared 5-aminosalicylates with placebo for maintenance of remission. The second systematic review reported no significant differences between 5-aminosalicylates and methotrexate for maintaining remission. Currently CG152 recommends thiopurines as first-line treatment for maintaining remission. Furthermore, methotrexate is recommended for patients who fail to respond to thiopurine therapy ([see 1.3.4 to 1.3.6](#)). In 1 systematic review, pooled analysis of 2 RCTs indicated no significant differences between maintenance of remission rates of patients treated by thiopurines and those treated by mesalazine. It was not possible to determine how many patients were included in the 2 RCTs. Thus, it was considered that additional evidence was needed to establish the role of mesalazine for maintenance of remission of Crohn’s disease.

New evidence is unlikely to change guideline recommendation

**152–17 What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission compared with**

- **usual diet?**
- **medical treatment?**
- **conventional glucocorticosteroid treatment?**
- **budesonide?**
- **5-ASA treatment?**
- **azathioprine or mercaptopurine?**
- **methotrexate?**

**Recommendations derived from this question**

Not linked to any guideline recommendations.

**Surveillance decision**

This review question should not be updated.

**2-year surveillance summary**

No relevant evidence was identified.

**4-year surveillance summary**

One systematic review<sup>44</sup> of 12 studies aimed to evaluate enteral feeding therapy for maintaining remission in Crohn's disease. Significant heterogeneity between identified studies precluded pooled analysis of data. Authors reported that 11 out of 12 studies reported that enteral nutrition was either better than, or as effective as, the comparator (not specified) in maintaining remission in patients with inactive Crohn's. No major serious adverse events were associated with enteral nutrition.

One systematic review<sup>45</sup> assessed the safety and efficacy of elemental nutrition for maintaining remission of Crohn's disease. Three of the identified RCTs reported that elemental nutrition was significantly better at maintaining remission than no nutrition at 24 month follow-up. Similarly, 3 identified non-randomised comparative studies reported that enteral nutrition was significantly better than no

nutrition at maintaining remission at 12 to 48 months and preventing relapse at 12 follow-up. No significant difference in mucosal healing rates were reported between intervention and control groups. Authors noted that adherence rates were significantly worse in patients treated by elemental nutrition than those treated by polymeric nutrition. When elemental nutrition was compared with other active treatments (medications, polymeric nutrition or a combination) no significant differences in adherence rates were observed between groups. Insufficient data on adverse events was available to pool data from identified studies. None of the studies explored the cost-effectiveness of elemental nutrition.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

No studies were identified during the 2-year surveillance review. One systematic review, identified during the 4-year surveillance review,

highlighted potential benefits of enteral nutrition but it was unclear what comparators were used in included studies. A second systematic review of 3 RCTs compared enteral nutrition with no enteral nutrition: no comparisons were made with medical intervention. Topic experts did not provide any feedback related to this clinical question. As a result it was considered that

more research, evaluating the comparative effectiveness of enteral nutrition, was needed before guideline recommendations were updated.

New evidence is unlikely to change guideline recommendations.

## **152–18 What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission in combination with**

- **conventional glucocorticosteroid treatment?**
- **Budesonide?**
- **5-ASA treatment?**
- **azathioprine or mercaptopurine?**
- **methotrexate?**
- **compared with any of the above?**

### **Recommendations derived from this question**

Not linked to any guideline recommendations.

### **Surveillance decision**

This review question should not be updated.

### **2-year surveillance summary**

No relevant evidence was identified.

### **4-year surveillance summary**

One systematic review<sup>46</sup> of 4 studies compared continued remission in patients treated by enteral nutrition plus infliximab and patients treated by infliximab-alone. Analysis revealed that enteral nutrition plus infliximab was significantly superior to infliximab-alone for maintaining remission at 1 year follow-up.

### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

### **Impact statement**

No new evidence was identified during the 2-year surveillance review. In 1 systematic review

identified in the 4-year surveillance review, authors reported that enteral nutrition plus infliximab combination therapy was superior to infliximab monotherapy for maintenance of remission of Crohn's disease. Currently CG152 does not make any recommendations about enteral nutrition combination therapy for maintenance of remission of Crohn's disease. Furthermore, no feedback was received from topic experts. As a result it was considered that more research, evaluating enteral nutrition combination therapy, was needed before guideline recommendations were expanded to include infliximab.

New evidence is unlikely to change guideline recommendations.

## Maintaining remission in Crohn's disease after surgery

**152–19 In adults and children what is the clinical and cost effectiveness of post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer of**

- **conventional glucocorticosteroid treatment**
- **budesonide**
- **5-aminosalicylate treatment**
- **azathioprine**
- **mercaptopurine**
- **methotrexate**
- **metronidazole or**
- **combinations thereof**
- **or nutritional treatment**

**compared with**

- **placebo**
- **no treatment?**

### Recommendations derived from this question

- 1.4.1 Consider azathioprine or mercaptopurine 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). [2012]
- 1.4.2 Consider 5-ASA treatment to maintain remission after surgery. [2012]
- 1.4.3 Do not offer budesonide or enteral nutrition to maintain remission after surgery. [2012]

### Surveillance decision

This review question should be updated.

#### 2-year surveillance summary

One RCT<sup>47</sup> assessed drug treatments in preventing relapse in people undergoing surgical resection of ileal or ileocolonic Crohn's disease. 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), and with 9 of 18 people (50%) in the mesalazine group (OR, 0.143). The results of this study add to those of a previous RCT<sup>48</sup> (n=24) of infliximab for prevention of recurrence 1 year after surgery. Infliximab was significantly better than placebo

for endoscopic recurrence and histological recurrence, but not for clinical remission.

#### 4-year surveillance summary

One network meta-analysis<sup>49</sup> of 15 studies compared the safety and efficacy profiles of 5-aminosalicylates, immunomodulators (azathioprine and mercaptopurine) and biologics for the prevention of postoperative recurrence in Crohn's disease. Authors reported that biologic agents significantly improved clinical and endoscopic recurrence rates compared with 5-aminosalicylates, immunomodulators, or placebo. Immunomodulators significantly improved

clinical and endoscopic recurrence rates compared with 5-aminosalicylates or placebo. However, immunomodulators were associated with significantly higher adverse event rates. Compared with placebo, 5-aminosalicylates were significantly better at prevention of clinical recurrence, without increasing the rate of adverse events.

In another network meta-analysis<sup>50</sup> investigators pooled data from 21 RCTs (including 2,006 patients) that compared the abilities of mesalazine, antibiotics, budesonide, immunomodulators, anti-TNF medications (started within 3 months of surgery), or placebo to prevent clinical and endoscopic relapse of Crohn's disease after surgical resection. Results indicated that mesalazine, antibiotics, immunomodulatory monotherapy, immunomodulatory plus antibiotics and anti-TNF medications significantly reduced the risk of clinical relapse compared to placebo. No significant difference in relapse rates was observed between patients treated by budesonide and those who received placebo. In relation to endoscopic relapse antibiotics, immunomodulatory monotherapy, immunomodulatory plus antibiotics and anti-TNF medications significantly reduced the risk of relapse compared to placebo but mesalazine and budesonide did not. Authors noted that anti-TNF therapy was the most effective intervention for postoperative intervention. Although this study indicated that the guideline should be updated, numerous limitations were identified. First, immunosuppressants and corticosteroids were used as concomitant treatment by some or all patients in included studies: proportions in each study were not reported. When outcomes were reported for multiple doses of medication, authors combined data for all doses: no justification was provided for this approach. Insufficient details about patient demographics were provided by authors. For example, minimal information on smoking, disease location, Crohn's disease phenotype, and number of previous surgeries was reported by authors. There was a limited number of studies comparing active medications with each other; importantly very few patients had anti-TNFs. The surveillance team also noted issues with the way the study was reported. Authors did not provide tabulated rank probabilities. Furthermore, there were inconsistencies identified in the model. It appears that inconsistencies were not explored and no

goodness of fit data was reported in the study manuscript.

One systematic review<sup>51</sup> of 7 RCTs aimed to assess the safety and efficacy of azathioprine and 6-mercaptopurine for maintenance of remission after surgical resection. One identified study reported no significant differences in clinical and endoscopic relapse rates in patients treated by azathioprine and those treated by infliximab. Another study reported significantly higher relapse rates in patients treated by azathioprine compared to those treated by adalimumab. Pooled analysis of 2 RCTs indicated that treatment with azathioprine or 6-mercaptopurine was significantly superior to placebo for reducing clinical relapse rates at 1 and 2 year follow-up assessments. Pooled analysis of 5 RCTs revealed no significant differences in relapse rates between patients treated by azathioprine or 6-mercaptopurine and those treated by 5-aminosalicylates at 1 and 2 years follow-up. When analysis was stratified according to type of purine analogue, no significant difference in clinical relapse rates was observed between azathioprine and 5-aminosalicylates at 1 year follow-up whereas 6-mercaptopurine was found to be significantly superior to 5-aminosalicylates at 2 year follow-up. Pooled data from 5 studies revealed that rates of withdrawal due to adverse events were significantly higher in patients treated by azathioprine or 6-mercaptopurine compared to those treated by 5-aminosalicylates. Authors stated that comparisons of rates of withdrawal due to adverse events between purine analogues and placebo were uncertain. Commonly reported adverse events across all studies included leukopenia, arthralgia, abdominal pain or severe epigastric intolerance, elevated liver enzymes, nausea and vomiting, pancreatitis, anaemia, exacerbation of Crohn's disease, nasopharyngitis, and flatulence.

In 1 systematic review<sup>52</sup> of 9 RCTs, investigators assessed the efficacy of anti-TNF-alpha therapy for maintenance of remission after surgery. Authors reported clinical recurrence was significantly less likely to occur in patients treated by anti-TNF therapy than controls (not specified). Additionally, Anti-TNF therapy was more effective than control arms at treating endoscopic postoperative recurrence.

In another systematic review<sup>53</sup> authors compared the efficacy of anti-TNF therapy with

that of conventional therapy (immunomodulators, mesalazine or placebo) for maintenance of remission of Crohn's disease after surgery. A significantly higher proportion of patients treated by anti-TNF therapy were in clinical remission at 1 year follow-up compared to those treated by conventional treatment. Furthermore, rates of endoscopic remission and histologic remission were reported in the anti-TNF therapy group.

One systematic review<sup>54</sup> compared outcomes of patients who received biological therapy (not specified) after surgery and those who did not. Authors reported that treatment with biologics significantly increased the risk of infectious complications and wound infections. No significant differences in rates of anastomotic leak, abdominal sepsis and reoperation were observed between patients who received postoperative biologic therapy and those who did not.

A systematic review<sup>55</sup> of 14 studies which assessed postoperative recurrence of patients with Crohn's treated by anti-TNF agents (not specified) reported that clinical and endoscopic recurrence rates were significantly lower in patients treated by anti-TNF agents than those treated by non-biologic agents (not specified). Furthermore, severe endoscopic recurrence rates were significantly lower in the anti-TNF therapy group.

Results from another systematic review<sup>56</sup> highlighted increased risks of postoperative complications, and infectious or anastomosis-related complications in patients who received anti-TNF therapy (not specified) after surgery.

In 1 systematic review<sup>57</sup> of 7 studies investigators assessed the safety and efficacy of biologic medicines (not specified) for the prevention of postoperative recurrence of Crohn's disease. Pooled data from RCTs indicated that biologic therapy significantly reduced the risks of postoperative clinical, endoscopic and severe recurrence compared to control arms (not specified). No significant difference in clinical recurrence rates were observed between patients treated by biologics and those treated by azathioprine. Conversely, endoscopic recurrence rates were significantly lower in patients treated by biologics than those treated by azathioprine. Compared to the control group, no significant difference in adverse events was observed in the biologic therapy group. A significantly greater proportion of patients in the anti-TNF therapy group had

maintained clinical remission. No significant difference in adverse event rates were reported between groups.

One systematic review<sup>58</sup> of 24 studies assessed outcomes of patients with fistulising perianal Crohn's disease treated by medical therapy- (anti-TNF-alpha therapies with or without immunomodulators) or surgical treatment alone compared with patients treated by surgery plus medical therapy. Complete remission was reported in 43% of patients in the monotherapy group and 52% of patients in the combination therapy group. No response was reported in 34% of patients in the monotherapy group and 23% of patients in the combination therapy group.

In 1 RCT<sup>59</sup> investigators assessed the efficacy of early colonoscopy at 6 months (active care) or no colonoscopy (conventional care) in patients who received medical therapy after intestinal resection. All patients received 3 months of metronidazole therapy after surgery. Patients at high risk of recurrence received an immunomodulator or adalimumab if they were intolerant to immunomodulators. Of 122 patients who received active care 39% (n=47) had endoscopic recurrence at 6 month follow-up and had their drug regimens stepped-up to immunomodulator, fortnightly adalimumab plus immunomodulator, or weekly adalimumab. Of those in remission at 6 months who did not change therapy, recurrence was reported in 41% (31/75) of patients at 12 month follow-up.

At 18 month follow-up endoscopic recurrence was observed in significantly fewer patients in the active care group. Maintained complete mucosal normality was reported in a significantly higher proportion of patients in the active care group. Authors reported that smoking and the presence of 2 or more clinical risk factors, including smoking, increased the risk of endoscopic recurrence. No significant difference in adverse event rates was reported between groups.

In an RCT<sup>60</sup> of 297 patients with Crohn's disease treated by infliximab or placebo, after ileocolonic resection, no significant difference in clinical recurrence rates were observed between groups at 76 week follow-up. The endoscopic recurrence rate was significantly lower in the infliximab group compared to the placebo group at 76 week follow-up. Subgroup analysis revealed that patients who had previously been treated by anti-TNF agents

and those with one or more resection had higher rates of clinical recurrence.

In 1 small RCT<sup>61</sup> 24 patients with Crohn's disease were randomised to receive infliximab or placebo, for 1 year after ileocolonic resection, and were followed up for 5 years. A significantly longer mean time to first endoscopic recurrence was reported in the infliximab group. Endoscopic recurrence rates were significantly lower in the infliximab group. Furthermore, the rate of additional surgery and the mean time to additional surgery were significantly longer in the infliximab group.

One RCT<sup>62</sup> compared the efficacy of systemic versus endoscopy-driven azathioprine therapy for preventing recurrence of Crohn's disease in 63 patients who underwent curative resection with ileocolonic anastomosis. Patients were randomised to systematic azathioprine, initiated less than 2 weeks after surgery, or endoscopy-driven azathioprine therapy which was only initiated after endoscopic recurrence. Authors reported that the study was prematurely stopped due to low recruitment and high dropout rates. Analysis of data from evaluable patients revealed no significant difference between systemic and endoscopy-driven azathioprine therapy.

#### **Topic expert feedback**

Topic experts suggested an RCT<sup>63</sup> which assessed the recurrence of Crohn's disease in patients who received mercaptopurine or placebo after surgical resection. Clinical recurrence of Crohn's was reported in 13% of patients in the mercaptopurine group and 23% of patients in the placebo group; however the differences between groups were not statistically significant. In a subgroup analysis 10% of smokers in the mercaptopurine group and 46% of smokers in the placebo group had a clinical recurrence that needed treatment. In relation to non-smokers, recurrence rates were 13% in the mercaptopurine group and 16% in the placebo group. This result was statistically significant. No significant differences in recurrence rates were observed between groups in other subgroup analyses: previous immunomodulator therapy, previous infliximab or methotrexate, previous surgery, duration of disease, or age at diagnosis. Furthermore, no significant difference in adverse event rates was reported between groups.

Topic experts felt that this study demonstrated that mercaptopurine is effective in preventing

postoperative clinical recurrence in patients who are smokers.

#### **Impact statement**

The evidence identified during the 2-year surveillance review indicated that adalimumab may be more effective than azathioprine or mesalazine in maintaining remission of Crohn's disease after surgery. However due to the small sample size of the RCT the review question was not updated.

Two network meta-analyses and 1 systematic review identified during the 4-year surveillance review highlighted potential benefits of using immunomodulators (azathioprine and 6-mercaptopurine) for maintenance of postoperative remission of Crohn's disease. Some systematic reviews, identified during the 4-year surveillance review, evaluated the efficacy of 5 aminosalicylates, and reported no significant difference in relapse rates compared to immunomodulators. Authors also reported significantly higher adverse event rates in patients treated by immunomodulators compared to those treated by 5 aminosalicylates. Overall these findings were largely in line with guideline recommendations.

A considerable amount of evidence (systematic reviews and RCTs) was identified which assessed the efficacy of anti-TNF therapy for maintenance of remission of Crohn's disease after surgery. Some of the evidence reported favourable outcomes associated with anti-TNF therapy, with some studies reporting that anti-TNF therapy was superior to immunomodulator therapy for postoperative maintenance of remission. Topic experts commented that the new evidence on the use of biologics after surgery increasingly reflects current practice.

Currently, NICE CG152 makes recommendations on the use of immunomodulators and 5-aminosalicylates following surgically-induced remission of Crohn's disease but no recommendations are made on the post-surgical use of biologic medicines. The licensed use of infliximab and adalimumab is covered by NICE TA187, but with no reference to post-surgical use of the agents. It was considered that this question should be updated to clarify the use of biologics to maintain remission of Crohn's disease after surgery. Note: This would include a partial update of technology appraisal guidance Infliximab and adalimumab for the treatment of Crohn's disease (2010) TA187 in the context of the clinical guideline. The update would cover



the use of infliximab and adalimumab for post-surgical maintenance of remission.

**New evidence identified that may change current recommendations.**

## Surgery

**152–20 In individuals diagnosed with Crohn’s disease limited to the distal ileum, what is the clinical and cost-effectiveness of surgical resection for induction and maintenance of remission compared with medical or nutritional treatment?**

### Recommendations derived from this question

#### *Crohn’s disease limited to the distal ileum*

- 1.5.1 Consider surgery as an alternative to medical treatment early in the course of the disease for people whose disease is limited to the distal ileum, taking into account the following:
- benefits and risks of medical treatment and surgery
  - risk of recurrence after surgery
  - individual preferences and any personal or cultural considerations.
- Record the person’s views in their notes.
- 1.5.2 Consider surgery early in the course of the disease or before or early in puberty for children and young people whose disease is limited to the distal ileum and who have:
- growth impairment despite optimal medical treatment and/or
  - refractory disease.
- Discuss treatment options within the multidisciplinary team and with the person’s parent or carer and, if appropriate, the child or young person. [2012]

### Surveillance decision

This review question should not be updated.

#### 2-year surveillance summary

No relevant evidence was identified.

#### 4-year surveillance summary

In 1 RCT<sup>64</sup> investigators assessed outcomes of 36 patients with ileocaecal Crohn’s disease treated by medical therapy (budesonide and maintenance treatment with azathioprine) or ileocaecal resection. No significant difference in Crohn’s disease activity index scores was observed between groups. At 1 year follow-up, SF-36 scores were significantly higher in patients who underwent surgery compared to those who received medical therapy.

One systematic review<sup>65</sup> of 8 studies aimed to compare surgical outcomes of stapled side-to-side anastomosis (SSSA) and hand sewn end-

to-end anastomosis (HEEA) in ileocolic resection for Crohn’s disease. Overall significantly fewer postoperative complications were reported in the SSA group. The proportions of patients with anastomotic leak, recurrence and those who needed reoperation for recurrence were significantly lower in the SSSA group. No significant differences in postoperative hospital length of stay, mortality rates, and complications, other than anastomotic leak, were observed between groups.

One RCT<sup>66</sup> of 108 patients assessed the potential benefits of preoperative nutrition on outcomes of surgery for Crohn’s disease. Patients received preoperative nutrition and were randomised to receive surgery after

achieving one of two different preoperative nutrition endpoints: improvement in malnutrition (IOM) or reduction of inflammation (ROI). After nutritional therapy serum C-reactive protein, Crohn's disease activity index scores and serum albumin levels improved in both study arms. Patients in the IOM group had significantly greater albumin levels and body weight gain than patients in the ROI group. No significant differences in rates of postoperative complications, faecal diversion, and postoperative recurrence were observed between groups.

#### Topic expert feedback

Topic experts suggested that the general indications for surgery set out in the original guideline have not changed. One expert highlighted that the guideline does not mention minimally invasive surgery. They stated that laparoscopic surgery is becoming standard care for patients who require surgery for Crohn's disease. Furthermore, the expert highlighted that there is an ongoing debate as to whether early surgery is better than continued medical treatment in selected patients with terminal ileal Crohn's disease.

#### Impact statement

No new studies were identified during the 2-year surveillance review. During the 4-year

surveillance review, 1 RCT was identified which reported no significant differences in Crohn's disease activity index scores of patients treated by medical therapy or ileocaecal resection. Insufficient details about the indications for surgical treatment were provided in the abstract. One of the identified studies compared 2 different surgical approaches whereas the other study evaluated potential benefits of perioperative nutrition on postsurgical outcomes. No comparisons were made with medical management for maintenance of remission. As a result, the identified new evidence is unlikely to have an impact on guideline recommendations.

Topic experts suggested that the general indications for surgery set out in the original guideline have not changed. One topic expert proposed that the guideline could mention minimally invasive surgery. No studies were identified assessing the efficacy the comparative effectiveness of minimally invasive surgery.

New evidence is unlikely to change guideline recommendations.

### 152–21 In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of surgical treatment of stricture compared

- with balloon dilation?
- balloon dilation plus intralesional glucocorticosteroid injections,
- conservative management?

#### Recommendations derived from this question

##### Managing strictures

- 1.5.3 Consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy. [2012]
- 1.5.4 Discuss the benefits and risks of balloon dilation and surgical interventions for managing strictures with:
  - the person with Crohn's disease and/or their parent or carer if appropriate and
  - a surgeon and
  - a gastroenterologist. [2012]
- 1.5.5 Take into account the following factors when assessing options for managing a stricture:
  - whether medical treatment has been optimised

- the number and extent of previous resections
  - the rapidity of past recurrence (if appropriate)
  - the potential for further resections
  - the consequence of short bowel syndrome
  - the person's preference, and how their lifestyle and cultural background might affect management. [2012]
- 1.5.6 Ensure that abdominal surgery is available for managing complications or failure of balloon dilation. [2012]

## Surveillance decision

This review question should not be updated.

### 2-year surveillance summary

No relevant evidence was identified.

### 4-year surveillance summary

In a systematic review<sup>67</sup> of 24 studies investigators assessed outcomes of patients who were treated endoscopic balloon dilation for Crohn's disease strictures. Authors reported that the surgical intervention rate was 27% over a median follow-up period of 15 to 70 months. The surgical intervention rate after dilation was 18% for anastomotic strictures compared to 29% for primary strictures (not significant). Authors reported that stricture lengths less than 4 cm were associated with a significantly lower risk of surgical intervention. Severe adverse events were reported in 4% of patients.

A systematic review<sup>68</sup> of 25 studies aimed to assess the symptomatic response (obstructive symptom-free outcome) and technical response (post-dilatation passage of the endoscope through a stricture) of patients treated by endoscopic balloon dilatation for Crohn's disease strictures. The symptomatic response rate was 70.2% whereas the technical response rate was 90.6%. Authors reported that pooled unweighted symptomatic response and technical response rates for de novo strictures were 45% and 84% respectively. Symptomatic response and technical response rates for anastomotic strictures were 58% and 84% respectively. The overall rates of complications and perforations were 6.4% and 3% respectively. Pooled unweighted complication and perforation rates for de novo strictures were 15% and 9% respectively, whereas pooled unweighted complication and

perforation rates for anastomotic strictures were 22% and 5%.

### Topic expert feedback

Topic experts suggested that the general indications for surgery set out in the original guideline have not changed. One expert highlighted that the guideline does not mention minimally invasive surgery. They stated that laparoscopic surgery is becoming standard care for patients who require surgery for Crohn's disease. Furthermore, the expert highlighted that there is an ongoing debate as to whether early surgery is better than continued medical treatment in selected patients with terminal ileal Crohn's disease.

### Impact statement

No new studies were identified during the 2-year surveillance review. The 2 systematic reviews identified during the 4-year surveillance review assessed the efficacy of balloon dilatation of Crohn's disease strictures, however no comparisons were made with surgical treatment. As a result they are unlikely to affect guideline recommendations.

Topic experts suggested that the general indications for surgery set out in the original guideline have not changed. One topic expert proposed that the guideline could mention minimally invasive surgery; however, literature searches did not yield any studies assessing the efficacy the comparative effectiveness of minimally invasive surgery.

New evidence is unlikely to change guideline recommendations.

## Monitoring

### **152–22 In children and young people with Crohn's disease what is the risk of fracture?**

#### **Recommendations derived from this question**

Refer to the NICE guideline on osteoporosis: assessing the risk of fragility fracture (NICE guideline CG146) for recommendations on assessing the risk of fragility fracture in adults. Crohn's disease is a cause of secondary osteoporosis.

- 1.6.1 Do not routinely monitor for changes in bone mineral density in children and young people. [2012]
- 1.6.2 Consider monitoring for changes in bone mineral density in children and young people with risk factors, such as low body mass index (BMI), low trauma fracture or continued or repeated glucocorticosteroid use. [2012]

#### **Surveillance decision**

This review question should not be updated.

#### **2-year surveillance summary**

One retrospective study<sup>69</sup> explored risk factors of for osteoporosis in adults with Crohn's disease (64%) or ulcerative colitis (34%) attending a single centre in the USA for treatment of inflammatory bowel disease. The 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 study reported that a BMI threshold of less than 21 kg/m<sup>2</sup> was a risk factor for osteoporosis.

#### **4-year surveillance summary**

No relevant evidence was identified.

#### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

#### **Impact statement**

It was considered that the studies identified during the 2-year surveillance review were

consistent with guideline recommendations.

The study reported that a BMI threshold of less than 21 kg/m<sup>2</sup> was a risk factor for osteoporosis. This was not consistent with NICE's definition of low body weight, which is a BMI less than 18.5 kg/m<sup>2</sup>. The study also highlighted that a low BMI may be the most important risk factor for osteoporosis in people with Crohn's disease. This evidence was considered to be broadly consistent with current guidance in NICE CG152 and NICE CG146.

No studies were identified and no feedback related to this clinical question was received from topic experts during the 4-year surveillance review. As a result, no new evidence was identified indicating that this question should be updated.

New evidence is unlikely to change guideline recommendations.

## 152–23 Does predicting early relapse through monitoring

- **Unintended weight loss**
- **CRP**
- **ESR**
- **MRI**
- **Calprotectin**
- **Colonoscopy/capsule endoscopy or**
- **Growth in children**

**compared with standard care, improve patient outcomes (quality of life, future surgery, hospitalisation)?**

### Recommendations derived from this question

Not linked to any guideline recommendations.

### Surveillance decision

This review question should not be updated.

#### 2-year surveillance summary

No relevant evidence was identified.

#### 4-year surveillance summary

One systematic review<sup>70</sup> aimed to assess whether endoscopic mucosal healing was predictive of favourable outcomes in patients with inflammatory bowel disease. Subgroup analysis of Crohn's disease studies indicated that mucosal healing was significantly associated with fewer abdominal surgeries and increased remission rates (no comparators were specified). Authors stated that complete remission and partial remission conferred significantly higher rates of favourable outcomes. Furthermore, they stated that complete healing was superior in predicting corticosteroid free remission.

In 1 systematic review<sup>71</sup> investigators assessed the usefulness of endoscopic scoring indices for evaluating disease activity in patients with Crohn's disease. One identified study reported that the Simple Endoscopic Scale for Crohn's Disease (SES-CD) had an intra-class correlation coefficient of 0.9815 and the kappa for the regions is high. Another study reported that the intra-class correlation coefficient of the Crohn's Disease Endoscopic Index of Severity (CDEIS) was 0.985 for average measures of video score and 0.835 for single measures of

video score. In relation to validity, 1 study reported that the correlation between CDEIS scores and C-reactive protein measurements was 0.521, whereas 2 other studies correlation coefficients of 0.553 and 0.608. One study reported the correlation coefficient between SES-CD and C-reactive protein was 0.46 whereas another study reported a coefficient of 0.68. Seven studies reported statistically significant improvements in CDEIS scores when patients received a treatment that was known to be efficacious. Additionally, 2 studies were identified which reported statistically significant improvements in SES-CD scores when patients received a treatment that was known to be efficacious.

In 1 RCT<sup>72</sup> investigators compared the usefulness of different faecal inflammatory markers (faecal calprotectin [FC], lactoferrin [FL], and S100A12 [FS]) for monitoring the status of Crohn's disease in 135 patients who underwent surgery. In all patients FC, FL and FS levels were elevated prior to surgery. Six months after surgery median biomarker levels decreased. Patients with recurrent disease had significantly higher levels of FC and FL than those without recurrent disease. No significant difference in FS levels were observed between patients with recurrent disease and those without. FC levels greater than 135 mug/g, FL

levels greater than 3.4 mug/g, and FS levels greater than 10.5 mug/g indicated endoscopic recurrence. Those cut-off concentrations yielded a sensitivity of 87%, 70% and 91% for FC, FL and FS respectively. The specificities of FC, FL and FS were 66%, 68% and 12%, respectively. The negative predictive values of FC, FL and FS were 91%, 81% and 71%, respectively. Authors stated that a significant correlation between FC and FL levels correlated and the presence and severity of endoscopic recurrence was observed, whereas no correlation was observed with FS and C-reactive protein levels, as well as Crohn's disease activity index scores.

In an RCT<sup>73</sup> of 135 patients who underwent intestinal resection, FC levels, C-reactive protein measurements and Crohn's disease activity index scores were recorded before surgery and at 6-monthly intervals after surgery. Median FC levels decreased after surgery. At 6 months, patients with disease recurrence had significantly higher FC levels compared to patients without disease recurrence. A significant correlation between combined 6- and 18-month FC levels and the presence and severity of Crohn's disease recurrence was observed. No correlation between C-reactive protein levels and the presence or severity of Crohn's disease recurrence was observed. Furthermore, no correlation between changes in Crohn's disease activity index scores and the presence or severity of Crohn's disease recurrence was observed. FC levels greater than 100 mug/g detected endoscopic recurrence with 89% sensitivity, 58% specificity and a negative predictive value of 91%. At 6 month follow-up, FC levels less than 51 mug/g predicted maintenance of remission in patients with endoscopic remission. In patients with endoscopic recurrence at 6 month follow-up who had their treatment regimens stepped-up, FC levels decreased from 324 mug/g to 180 mug/g at 12 months and 109 mug/g at 18 months.

#### **Topic expert feedback**

Topic experts highlighted the potential benefits of using magnetic resonance enterography (MRE) and video capsule endoscopy (VCE) to characterise Crohn's disease. Experts suggested a cohort study<sup>74</sup> of patients who underwent small-bowel VCE or MRE or both. Previously unrecognised disease locations

were detected with VCE and MRE in 51% and 25%, respectively ( $p < 0.01$ ). When both modalities were combined the detection rate was 55%. MRE resulted in reclassification of phenotype in 26% of patients whereas VCE resulted in reclassification in 11% of patients ( $p < 0.05$ ). When both modalities were combined original Montreal classifications were reclassified in 64% of patients.

One topic expert felt that faecal calprotectin testing is a potentially useful test for diagnosing and monitoring Crohn's disease after surgery.

#### **Impact statement**

Literature searches yielded 2 systematic reviews which assessed the usefulness of endoscopy for evaluating disease activity. The first systematic review reported that endoscopic assessment was associated with fewer surgeries and higher rates of remission. However, it was not clear how many studies and patients were included in the analyses. The second systematic review did not pool data from identified studies and instead reported results from studies assessing different endoscopic scoring systems. Generally, the studies identified in the systematic review reported favourable outcomes associated with VCE; however, it was not possible to determine absolute measures of benefit.

Two publications were identified which assessed the potential benefits of faecal calprotectin testing in people with Crohn's disease who had undergone surgery. The 2 studies had identical sample sizes and were performed by the same group of investigators. Although the 2 studies highlighted some potential benefits of faecal calprotectin test, the study population comprised a subset of people with Crohn's disease; people who underwent surgery. Furthermore, outcomes reported in the identified studies are partially relevant to this clinical question. More research is needed to determine whether faecal calprotectin testing can improve patient outcomes in the wider population of people with Crohn's disease (quality of life, future surgery & hospitalisation).

Overall, it was considered that more research is needed to determine which methods of predicting early relapse yield the greatest benefits in patients with Crohn's disease.

New evidence is unlikely to change guideline recommendations.



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## Conception and pregnancy

### **152–24 What are the specific needs, if any, in pregnancy and females of child-bearing potential who have Crohn's disease?**

#### **Recommendations derived from this question**

- 1.7.1 Give 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. [2012]
- 1.7.2 Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gastroenterology) in the care of pregnant women with Crohn's disease. [2012]

#### **Surveillance decision**

This review question should not be updated.

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#### **2-year surveillance summary**

##### *Birth outcomes after TNF inhibitor treatment*

One systematic review<sup>75</sup> investigated birth outcomes in women with inflammatory bowel disease exposed to TNF inhibitors during pregnancy or up to 90 days before conception (n≥1533). 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, foetal 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.

##### *Birth outcomes after thiopurine treatment*

One systematic review<sup>76</sup> investigated whether thiopurine treatment in women (or men) before conception and during pregnancy was associated with adverse birth outcomes. In the 5 studies which assessed 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) or congenital malformations (OR, 1.45; 95% CI 0.99 to 2.13). 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). In 3 studies which assessed 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).

The study indicated 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 was considered to add to clinicians' awareness of the risks and benefits of TNF inhibitors in pregnancy but no impact on NICE CG152 was expected.

#### **4-year surveillance summary**

No relevant evidence was identified.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

It was considered that the studies identified during the 2-year surveillance review were unlikely to affect guideline recommendations. The evidence suggested that TNF inhibitors did not seem to be associated with major adverse effects when used during pregnancy. This evidence was considered to add to clinicians'

awareness of the risks and benefits of TNF inhibitors in pregnancy, but was unlikely to affect recommendations in NICE CG152. No studies were identified and no feedback related to this clinical question was received from topic experts during the 4-year surveillance review. As a result, no new evidence was identified indicating that this question should be updated.

New evidence is unlikely to change guideline recommendations.

**NQ – 01 What is the clinical and cost effectiveness of naltrexone for induction of remission?**

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

**Surveillance decision**

This question should not be added.

**2-year surveillance summary**

In a Cochrane review<sup>77</sup> of RCTs of low-dose naltrexone for inducing remission in Crohn's disease, 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).

**4-year surveillance summary**

No relevant evidence was identified.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

During the 2-year surveillance review, it was considered that there was no evidence to suggest that naltrexone was effective for inducing remission of Crohn's disease; therefore no impact on NICE CG152 was expected. No new evidence was identified and no topic feedback was received during the 4-year surveillance review. As a result, insufficient evidence is available to add this question to the guideline.

New evidence is unlikely to impact on the guideline.

**NQ – 02 What is the clinical and cost effectiveness of biologic therapies, other than infliximab, adalimumab and vedolizumab, for induction or maintenance of remission of moderate-to-severe Crohn's disease?**

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.



## Surveillance decision

This question should not be added.

NICE CG152 should cross-refer to the technology appraisal on [vedolizumab for treating moderately to severely active Crohn's disease after prior therapy](#) (TA352) and/or include TA352 in the list of related NICE guidance.

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### 2-year surveillance summary

No relevant evidence was identified

### 4-year surveillance summary

A network meta-analysis<sup>78</sup> of 23 RCTs compared the efficacy of anti-integrin therapy and anti-TNF therapy for induction and maintenance of remission of Crohn's. No significant difference was observed between anti-integrin and anti-TNF agents in relation to induction and maintenance of response. Similar results were observed when analysis was limited to patients who had not previously received anti-TNF therapy. No significant differences in adverse event, infection, and treatment discontinuation rates were observed between groups.

One network meta-analysis<sup>17</sup> of 17 RCTs assessed the comparative efficacy of biologic therapy in biologic-naïve patients with Crohn's disease. Authors reported that certolizumab pegol, and natalizumab were not likely to induce remission than placebo. Additionally, no significant difference in maintenance of remission rates were observed between certolizumab pegol, natalizumab, and placebo. Natalizumab and certolizumab are not licensed for treating Crohn's disease in the UK.

A systematic review<sup>79</sup> of 8 randomised controlled trials compared the safety and efficacies of natalizumab with that of placebo. In anti-TNF-naïve and anti-TNF exposed patients, natalizumab was significantly better at inducing remission of Crohn's compared with placebo.

In 1 systematic review<sup>80</sup> of 10 studies, authors reported a slight increase in remission rates of patients with Crohn's who received natalizumab compared with those who received placebo. Furthermore, although natalizumab conferred slight improvements in Crohn's disease activity index scores, the clinical response was less robust than that of the remission rate.

In a meta-analysis<sup>81</sup> of 15 studies which assessed the safety profile of certolizumab pegol in patients with moderate-to-severe Crohn's disease, certolizumab pegol was

associated with significantly higher rates of serious adverse events compared to placebo. The incidence rates of serious infections and malignancies among patients who received short-term treatment with certolizumab pegol were 8.49 per 100 patient-years and 1.01 per 100 patient-years, respectively.

In 1 RCT<sup>82</sup> 139 patients with Crohn's disease were randomised to receive tofacitinib 1 mg, 5 mg, or 15 mg, or placebo. No significant differences in clinical response rates and clinical remission rates were observed between groups at 4 week follow-up. Authors noted that patients in the tofacitinib 15 mg had reduced levels of C-reactive protein and faecal calprotectin at follow-up. No significant differences in adverse event and serious adverse event rates were reported between groups. Authors reported that increases in low- and high-density lipoprotein cholesterol were observed in patients given the tofacitinib 5 mg or 15 mg doses. Tofacitinib is not licensed for treating Crohn's in the UK.

Literature searches yielded 5 systematic reviews<sup>79,80,83-85</sup> and 1 RCT<sup>86</sup> which assessed the safety and/or efficacy of vedolizumab for treatment of Crohn's disease.

### Topic expert feedback

Topic expert feedback and external correspondence noted the publication of TA352 and suggested that NICE CG152 should cross-refer to TA352

### Impact statement

During this 4-year surveillance review, 1 large NMA reported no differences between anti-TNF therapy and anti-integrin therapy, highlighting that anti-integrins could be an effective treatment for Crohn's disease. Various limitations were identified with study design and analyses performed, making it difficult to determine the quality of the systematic review. As a result, it was considered that the study's results were unlikely to have an impact on guideline recommendations.

1 NMA of 17 RCTs reported that certolizumab pegol, and natalizumab reported no difference

in induction of remission compared to placebo. One smaller systematic review reported that natalizumab was significantly better at inducing remission compared with placebo, whereas another systematic review reported slightly higher remission rates associated with natalizumab therapy. The inconsistent results of the systematic reviews and NMA indicate that more research is needed to clarify the role of natalizumab for treating Crohn's disease.

In relation to tofacitinib, 1 RCT reported no significant differences in clinical response rates and clinical remission rates of patients treated by tofacitinib and those treated by placebo.

These results are unlikely to have an impact on the guideline.

The NICE technology appraisal team has been informed about all new evidence relating to drugs considered by technology appraisals. Overall, it was considered that there was insufficient evidence to add this question to NICE CG152 at this point in time. The clinical guideline will cross-refer to TA352 and/or include TA352 in the list of related NICE guidance.

New evidence is unlikely to impact on the guideline.

## Editorial and factual corrections identified during surveillance

During surveillance process topic experts noted the technology appraisal on [Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy](#) (TA352) which was published after NICE CG152 was published. It is proposed that NICE CG152 should cross-refer to TA352.

## Research recommendations

### *Prioritised research recommendations*

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). The research recommendations will remain in the full versions of the guideline. See NICE's [research recommendations process and methods guide 2015](#) for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision **will** be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 01 For patients with intestinal Crohn's disease, does the addition of azathioprine to glucocorticosteroid treatment at diagnosis improve the long-term outcome compared with glucocorticosteroid treatment alone?**

No new information was identified at any surveillance review.

**Topic expert feedback**

Topic experts highlighted this is an important area and high quality research would remove uncertainty in current practice.

**Surveillance decision**

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 02 What are the benefits, risks and cost effectiveness of enteral nutrition compared with glucocorticosteroid treatment in adults and children?**

No new information was identified at any surveillance review.

**Topic expert feedback**

Topic experts highlighted this is an important area and high quality research would remove uncertainty in current practice.

**Surveillance decision**

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 03 Following successful medical induction of remission of Crohn's disease of the colon, is mesalazine more clinically and cost effective than no treatment?**

**2-year surveillance summary**

No relevant evidence was identified.

**4-year surveillance summary**

One systematic review<sup>43</sup> of 12 studies assessed the safety and efficacy of oral 5-aminosalicylic acid for maintenance of remission of Crohn's disease. Investigators included RCTs which compared 5-aminosalicylates with either placebo or sulfasalazine. No studies comparing 5-aminosalicylates with sulfasalazine were identified. Pooled analysis of 11 studies indicated no significant difference in relapse rates of patients treated by 5-aminosalicylates or those who received placebo at 12 month follow-up. One identified study reported no significant difference between 5-aminosalicylates and placebo at 24 month follow-up. Another study, which focussed on children with Crohn's disease, reported no significant difference in relapse rates between the 5-aminosalicylate group and the placebo group at 12 month follow-up. No significant differences in adverse event and serious adverse event rates were observed between groups. Furthermore, no significant differences in rates of withdrawal due to adverse events were observed between groups. Common adverse events reported in the studies included diarrhoea, nausea and vomiting, abdominal pain, headache and skin rash.

### **Topic expert feedback**

One topic expert suggested that the role of mesalazine in treating Crohn's disease is disputable. No studies were suggested.

### **Impact statement**

New evidence was identified comparing mesalazine with placebo; however, there was no indication from the study abstract that participants had Crohn's disease limited to the colon. Although this study demonstrates research activity related to this research recommendation, there was insufficient evidence to trigger an update.

### **Surveillance decision**

The research recommendation will be retained because there is evidence of research activity in this area.

### **RR – 04 What is the effect on quality of life of medical treatment (immunosuppressive or biological therapy) compared with early surgery for Crohn's disease limited to the distal ileum?**

#### **2-year surveillance summary**

No relevant evidence was identified.

#### **4-year surveillance summary**

No relevant evidence was identified.

### **Topic expert feedback**

Topic experts suggested that the general indications for surgery set out in the original guideline have not changed. One expert highlighted that the guideline does not mention minimally invasive surgery. They stated that laparoscopic surgery is becoming standard care for patients who require surgery for Crohn's disease. Furthermore, the expert highlighted that there is an ongoing debate as to whether early surgery is better than continued medical treatment in selected patients with terminal ileal Crohn's disease.

### **Impact statement**

No new information was identified at any surveillance review. Although experts highlighted that the general indications for surgery haven't changed, they also stated that there is an ongoing debate as to whether early surgery is better than continued medical treatment in selected patients with terminal ileal Crohn's disease.

### **Surveillance decision**

This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

### **RR – 05 What are the information needs of people with Crohn's disease, as defined by people with the condition, and can education and support based on these needs lead to better clinical and quality of life outcomes?**

The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).

### Surveillance decision

The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 06 Does combined therapy of a tumour necrosis factor (TNF)-alpha inhibitor with an immunosuppressant improve clinical outcomes and reduce the risk of serious adverse events in adults and children (6–17 years) with severe, active Crohn’s disease who are starting a TNF-alpha inhibitor (infliximab or adalimumab) for the induction of remission, where previous conventional therapy has failed?**

No new information was identified at any surveillance review.

### Surveillance decision

This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database.

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