National Institute for Health and Care Excellence

FINAL

Crohn's disease: management

Evidence review for post-surgical maintenance of remission

NICE guideline NG129

Evidence review

May 2019

Final

This evidence review was developed by the NICE Guideline Updates Team

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ISBN: 978-1-4731-3390-7

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Post-surgical maintenance of remission

Review question

In adults and children what is the clinical and cost effectiveness of medical and/or nutritional treatment for post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer?

Introduction

Crohn's disease is a long-term condition characterised by inflammation of the lining of the digestive system. Typically people with Crohn's disease have recurrent acute exacerbations ('flares') interspersed with periods of remission or less active disease. Incidence of Crohn's disease is greatest in people aged between 15 and 30 years. However it may affect people of any age: 15% are older than 60 years at diagnosis while 20–30% are younger than 20 years. Crohn's disease is not medically or surgically curable. The aim of treatment is to supress the inflammatory process, provide symptom relief, and maintain or improve quality of life while minimising short- and long-term adverse effects. Clinical management depends on disease activity, site, and behaviour (inflammatory, stricturing or fistulising), response to previous medications, and extra-intestinal symptoms. Current treatment includes aminosalicylates, corticosteroids, immunosuppressants, certain biologic agents, antibiotics, nutritional supplementation and dietary measures.

The 2012 NICE guideline for the management of Crohn's disease (CG152) covers strategies for treating acute disease (to induce remission) and for preventing relapse (maintaining remission). This update is concerned with maintaining remission after surgery.

In 2017, the NICE Surveillance team reviewed evidence on the maintenance of remission in Crohn's disease after surgery. New evidence was found for the treatment options included in the review and for new treatment options, specifically biologic medications. This review aims to consider pharmocologoical treatments including: aminosalicylates, immunomodulators, biologics and budesonide. This review also aims to consider enteral nutrition in the maintenance of remission after surgery. Please refer to the PICO table for a summary of conditions specified for this evidence review. For full details of the review protocol, see Appendix A:.

PICO table

Population	Patients of all ages who have had intestinal surgery within the last three months for active Crohn's disease.
Interventions	Post-surgical medical and/or enteral nutritional treatment: Oral budesonide Oral 5-aminosalicylates Oral azathioprine/mercaptopurine Methotrexate Metronidazole Mycophenolate Enteral nutrition Infliximab, adalimumab and biosimilars Vedolizumab and ustekinemab
Comparator	No treatment

	Placebo Each other Combinations of drugs

Outcomes	• Maintenance of remission (for 12 months or longer) as defined by:
	  ○ Absence of clinical symptoms (determined by investigator)
	  ○ Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy
	  ○ Harvey Bradshaw Index (HBI) < 3
	  ○ Endoscopic evaluation (Rutgeerts' score < i2)
	  ○ Faecal calprotectin
	• Serious adverse events
	  ○ Infection
	  ○ Poor wound healing
	• Withdrawal due to adverse events
	• Readmission/hospitalisation
	• Quality of life (including short QOL questionnaire, IMPACT 3 and IBD specific tools)

Protocol deviations

The committee specified that treatment with metronidazole would only be considered for 3 months after surgery and therefore, metronidazole was limited to 3 months only. This is because of concerns regarding adverse events associated with long-term metronidazole use.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in Appendix A:

Where needed, further support on the network-meta-analysis and health economic analysis was received from NICE's Technical Support Unit (TSU) at the University of Bristol.

For full details of methods and processes, including outcome selection, see Appendix B:

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Clinical evidence

Included studies

From the 2012 guideline, 10 relevant RCTs were identified and included. In 2017, a systematic literature search, which was combined with the 2013 ulcerative colitis: management guideline update, was carried out to identify randomised controlled trials. From 9,811 articles, 64 were deemed relevant to the review protocol and retrieved in full. Of these, 11 randomised controlled trials (RCTs) were included. In total, 21 RCTs were included. See Appendix C and Appendix D for further details.

A top-up search in August 2018 found 31 potentially relevant articles from 1,350 articles. Of these, no additional relevant RCTs were found. For full details of study identification, please see Appendix D: The search strategy is detailed in appendix C.

For full references of included studies, please see Appendix E:

Excluded studies

For full details of excluded studies with reasons for their exclusion, please see Appendix M.
For full references of excluded studies, please see Appendix E:

Summary of clinical studies included in the evidence review

Study	Population details	Intervention(s)	Comparison	Outcomes
Ardizzone 2004	N=140 Italy Adults patients who underwent 'conservative' surgery (strictureplasty) for Crohn's disease.	Mesalazine orally: 3 g/day in three divided doses N=71	Azathioprine orally: 2 mg/ kg/day N=69	- Clinical remission at 24 months (absence of symptoms, CDAI score < 200 and lack of endoscopic, radiologic and laboratory evidence of recurrence) - Withdrawal due to adverse events at 24 months
Armuzzi 2013	N=22 Consecutive Crohn's disease patients who underwent a curative ileocolonic resection and were considered to be at 'high risk' of postoperative recurrence. All patients received oral metronidazole (500 mg twice daily) for 2 weeks after surgery	Infliximab 5 mg/kg at weeks 0, 2 and 6 weeks and then every 8 weeks N=11	Azathioprine 2.5 mg/kg/day N=11	- Endoscopic remission at 12 months (Rutgeerts' score < i2) - Clinical remission at 12 months (HBI < 8) - Withdrawal due to adverse events at 12 months follow-up
Brignola 1995	N=87 Italy Patients with curative resection of Crohn's disease (i.e. removal of all macroscopic disease in ileal or ileocaecal region). Mean age in mesalazine: 39 + 17 Mean age in placebo: 34 + 10 more than 1 previous operation 13 vs. 11	Mesalazine (Pentasa) 2 x 500 mg tablets 3 times daily (i.e. 3 g/day) (n = 44)	Placebo (n = 43)	- Clinical remission at 12 months (CDAI < 150 and < 100 point increase from baseline) - Endoscopic remission at 12 months (Rutgeerts' score < i2) - Withdrawal due to adverse events at 12 months follow-up
Caprilli 1994	N=110 First intestinal resection Aged 18 to 65 years, disease limited to terminal ileum with or without involvement of caecum-	Mesalazine (Asacol) 2.4g/day N=55	No treatment. N=55	- Clinical remission at 12 months (CDAI < 150) - Endoscopic remission at 12 months (Rutgeerts' score = i0)

Study	Population details	Intervention(s)	Comparison	Outcomes
	ascending colon. Resection had to first and judged to be 'radical' (complete removal of macroscopically involved intestinal segment), absence of skip lesions; diagnosis of Crohn's disease confirmed macroscopically and microscopically by standard criteria.			- Withdrawal due to adverse events at 12 months follow-up
D'Haens 2008	N=81 Belgium Aged 18-70 years having curative ileal or ileocolonic resection with ileocolonic anastomosis for Crohn's disease. Classified as high risk for recurrence: 1 one more risk factors for the development of early/severe post-surgical recurrence (age < 30 years; active smoking; glucocorticosteroid use in the 3 months before surgery; 2nd, 3rd or 4th resection; perforating disease i.e. abscess or fistula as indication for surgery); women had to have negative pregnancy test and use adequate birth control.	Metronidazole 250 mg 3 times daily (or ornidazole 500 mg twice daily if metronidazole not tolerated) for three months + azathioprine (2 tablets [100 mg] if weight < 60 kg or 3 tablets [150 mg] if weight > 60 kg) for 12 months.	Metronidazole 250 mg 3 times daily (or ornidazole 500 mg twice daily if metronidazole not tolerated) for three months + placebo for 12 months.	- Clinical relapse at 12 months (CDAI < 250) - Endoscopic remission at 12 months (Rutgeerts' score < i2) - Withdrawal due to adverse events at 12 months follow-up
Ewe 1989	N=232 Germany Patients having resection for Crohn's disease (radical or non-radical resection as customary in each participating centre).	Sulfasalazine 3 g daily	Placebo	- Clinical remission at 12 and 24 months: CDAI score (not described) and blood tests
Ewe 1999	N=83 Germany Patients having curative resection for ileal, ileocolonic or colonic Crohn's disease and an anastomosis accessible to colonoscopy.	Budesonide 1 mg capsule 3 times daily N=43	Placebo N=40	- Clinical remission at 12 and 24 months: CDAI < 150 - Withdrawal due adverse events at 12 months follow-up
Hanauer 2004	N=131 USA 1st or subsequent ileocolic resection with primary	- Mesalazine (Pentasa) 3 g daily (n = 44)	Placebo (n = 40)	Mesalazine vs placebo, Mercaptopurine vs placebo and Mesalazine vs Mercaptopurine:

Study	Population details	Intervention(s)	Comparison	Outcomes
	anastomosis with disease confined to the ileum and adjacent colon.	-Mercaptopurine (50 mg) orally (n = 47)		- Clinical remission at 24 months: clinical examination - Endoscopic remission at 24 months (Rutgeerts' score = < i2) - Withdrawal due to adverse events at 24 months follow-up
Hellers 1999	N=129 Multicentre study in Sweden, France, England, Sweden, Germany, Italy, The Netherlands, Belgium Patients having resection for ileocolonic Crohn's disease	Budesonide controlled ileal release (CIR) 6 mg/day (Entocort) N=63	Placebo N= 66	- Clinical relapse at 12 months: CDAI < 200 - Endoscopic remission at 12 months (Rutgeerts' score = < i2) - Withdrawal due adverse events at 12 months follow-up
Lochs 2000	N=318 Multicentre trial: Austria, Germany, Denmark, Norway Patients 18-70 years of age who had respective surgery (radical i.e. no lesions left, or non-radical) for a Crohn's disease-specific lesion;	Mesalazine (Pentasa) 4g daily (divided into 3 doses of 1.5 g, 1 g and 1.5 g) n = 152	Placebo n = 166	- Clinical remission at 18 months: CDAI < 150 points and < 60 point increase in CDAI score - Endoscopic remission at 24 months (Rutgeerts' score = < i2)
Lopez-Sanroman 2017	N=91 Adults with clinically indicated and elective ileocolonic or ileocaecal resection.	Azathioprine 2.5 mg/kg/day + metronidazole 250 mg three times a day orally was added for the first 3 months.	Adalimumab 160 mg subcutaneously (SC), then 80 mg SC at Week 2, or 40 mg SC, at Week 4 and every 2 weeks thereafter. + metronidazole 250 mg three times a day orally was added for the first 3 months.	- Endoscopic remission at 24 months (Rutgeerts' score = < i2) - Clinical remission at 24 months: CDAI < 200 - Withdrawal due to adverse events at 24 months - Hospitalisation
Manosa 2013	N= 50 Spain Adults with CD undergoing ileal or ileocolic resection	Metronidazole (3 months) + azathioprine (2–2.5 mg/kg per day)	Placebo (3 months) + azathioprine (2–2.5 mg/kg per day)	- Clinical Relapse: Harvey–Bradshaw index of >7

Study	Population details	Intervention(s)	Comparison	Outcomes
	with ileocolic or ileorectal anastomosis.			- Endoscopic remission at 24 months (Rutgeerts' score = < i2) - Withdrawal due to adverse events at 12 months
McLeod 1995	N=163 USA and Canada Surgical resection for Crohn's disease; no gross residual disease; randomised within 8 weeks of surgery	Mesalazine 3 g/day (Rowasa I or Salofalk) n = 87	Placebo n = 76	- Clinical remission at 36 months (72 months maximum) follow-up: clinical examination - Withdrawal due to adverse events at 72 months follow-up
Mowat 2016	N=240 UK Adults enrolled within 4 weeks of resection of macroscopically diseased bowel with anastomosis between normal ileum and colon (ie, ileocolonic anastomosis).	Mercaptopurine, 1 mg/kg rounded to nearest 25mg)	Placebo	- Clinical remission at 36 months (CDAI < 150, < 100 point increase from baseline and lack of anti-inflammatory rescue treatment) - Endoscopic remission at 36 months (Rutgeerts' score < i2) - Adverse events: infection, 36 months follow-up - Withdrawal due to adverse events at 36 months
Regueiro 2009	N=24 USA Adults with Crohn's disease who underwent a curative resection of the distal ileum and partial colectomy with ileocolonic resection for complications of ileal Crohn's disease	Infusions of infliximab 5 mg/kg at 0, 2, and 6 weeks, followed by every 8 weeks for 54 weeks. N=11	Placebo N=13	- Clinical remission at 12 months (CDAI < 150) - Endoscopic remission at 12 months (Rutgeerts' score < i2) - Hospitalisation - Withdrawal due to adverse events at 12 months
Regueiro 2016 (PREVENT trial)	N=297 104 sites worldwide At least 18 years old with a confirmed diagnosis of CD who had undergone	Infliximab 5 mg/kg every 8 weeks. N=147	Placebo every 8 weeks N=150	- Endoscopic remission at 17.5 months (Rutgeerts' score < i2) - Clinical and endoscopic remission at

Study	Population details	Intervention(s)	Comparison	Outcomes
	ileocolonic resection with ileocolonic anastomosis. An end or loop ileostomy within 1 year was permitted if stoma closure and ileocolonic anastomosis occurred within 45 days of randomization Patients were also required to have a baseline CDAI score <200 and at least one of the following risk factors for disease recurrence: qualifying surgery that was their second intra-abdominal resection within 10 years; third or more intra-abdominal resection; resection for a penetrating CD complication (eg, abscess or fistula); a history of perianal fistulising CD, provided the event had not occurred within 3 months; or smoking 10 or more cigarettes per day for the past year. Concomitant therapy: Patients receiving oral mesalamine or immunosuppressives (azathioprine, 6-mercaptopurine, or methotrexate) pre-surgery could continue treatment with maintenance of stable doses after resection.			17.5 and 34 months (CDAI =< 200 and Rutgeerts' score < i2) - Severe adverse event: Infection and infestations - Hospitalisation - Withdrawal due to adverse events at 26 months follow-up
Rutgeerts 1995	N=57 Country not reported. Adults with first resection as well as patients who had undergone prior resections were included. The inflamed segment of ileum together with 5-15 cm of normal ileum were resected, and the anastomosis was constructed with uninvolved colon.	Metronidazole (20 mg/kg) daily for three months N=29 Therapy was started as soon as possible after surgery, immediately after refeeding and always within 1 week after resection.	Placebo N=28	- Clinical relapse at 12, 24 and 36 months (clinical assessment) - Endoscopic remission at 36 months (Rutgeerts' score i0) - Withdrawal due to adverse events at 36 months follow-up
Savarino 2013	N=51	Adalimumab 160/80 mg at weeks 0 and 2, followed by 40	Mesalazine 3 g/day N=18	- Adalimumab vs Azathioprine, - Adalimumab vs Mesalazine,

Study	Population details	Intervention(s)	Comparison	Outcomes
	Adult patients with ileal or ileocolonic CD undergoing resection.	mg every 2 weeks. N=16 Azathioprine 2.0 mg/kg/day. N=17		- Azathioprine vs Mesalazine: - Endoscopic remission at 12 months (Rutgeerts' score = < i2) - Endoscopic remission at 24 months (Rutgeerts' score = < i2) - Clinical remission at 12 months (CDAI <150) - Withdrawal due to adverse events - Hospitalisation - Quality of life at 2 years (IBD-Q > 170) - (score of 170 or more considered to be in remission)
Tursi 2014	N=20 considered at high risk of postoperative recurrence. Participants underwent curative ileocolonic resection and were considered to be at high risk of postoperative recurrence were enrolled. Intestinal resection was considered "curative" if all macroscopically inflamed tissues were removed and operative margins were disease-free at histopathology examination. Patients were considered at "high risk" for postoperative recurrence if they had 2 or more of the following risk factors: young age at diagnosis (≤30 years), penetrating disease, active smoking, perianal disease at diagnosis, previous surgery and <3 years from previous surgery.	Infliximab (5 mg/kg at 0, 2 and 6 weeks and then every 8 weeks). N=10	Adalimumab (160 mg subcutaneously, followed by 80 mg 2 weeks later, and then 40 mg every 2 weeks). N=10	- Endoscopic remission at 12 months (Rutgeerts' score = < i2)

Study	Population details	Intervention(s)	Comparison	Outcomes
Wenckert 1977	N=66 Inter-Nordic Cooperative Study Patients who were resected within one month of initiation of maintenance drug. - Median age of 24 ½ years. - The localisation at the time of operation was: jejunum 1, ileum 8, colon 15 and ileum + colon 42.	Salazosulfapyridine (Salazopyrin) 3 g/day	Placebo	- Clinical relapse at 12 months: clinical assessment - Clinical relapse at 18 months: clinical assessment
Yoshida 2012	N=31 Japan Aged between 12 and 65 with ileal or ileocolic CD within 4 weeks of undergoing macroscopic disease resection with anastomoses, which were side-to-side and stapled. Concomitant therapy: Oral mesalazine (pentasa) given to patients in both arms at same mean dose of 2.25 g/day Elemental diet less than 1200 kcal/day.	Infliximab 5 mg/kg at 8 week intervals. Participants did not receive loading dose at week 0, 2 and 6.	No intervention (participant continue with ongoing conventional medication (if any) that had started 8 weeks prior to surgery).	- Clinical remission at 12 and 36 months (CDAI < 150) - Endoscopic remission at 12 months (Rutgeerts' score < i2) - Severe adverse event: infection - Withdrawal due to adverse events at 36 months
CDAI: Crohn's Disease Activity Index; HBI: Harvey Bradshaw Index				

See Appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See Appendix F for full GRADE tables.

See the evidence tables in Appendix F: for quality assessment of individual studies and Appendix H: for full GRADE tables.

Economic evidence

Included studies

A search was conducted to identify economic evaluations published since the 2012 Crohn's disease guideline (Appendix C). The search returned 2,107 records, 1 of which had been identified in the previous guideline. Of the 2,107 records, 2,102 were excluded on the basis

of title and abstract. The remaining studies were reviewed by inspecting the full text and 2 published studies were included in the review.

A top up search was conducted in August 2018 and returned 240 additional records, all of which were excluded on the basis of title and abstract.

Excluded studies

Details of excluded studies with reasons for their exclusion are provided in Appendix M. For full references of excluded, please see Appendix E:.

Summary of studies included in the economic evidence review

The 2 published economic evaluations included in this review compared different drugs for maintenance of remission and are summarised in Table 1. Further details are available in Appendix K.

Ananthakrishnan 2011 conducted a cost-utility analysis to compare 5 strategies for maintenance of postoperative remission of Crohn's disease from a US third-party payer perspective. Costs and quality-adjusted life years (QALYs) were estimated over a 12-month time horizon to compare no treatment, azathioprine, metronidazole, upfront infliximab and infliximab initiated only if there was endoscopic evidence of disease at 6 months post-surgery (referred to as tailored infliximab). The model was structured using a decision tree. If clinical relapse occurred, people who had received no treatment, azathioprine or metronidazole as maintenance treatment were switched to infliximab. People who relapsed while receiving upfront infliximab maintenance treatment were assumed to receive azathioprine. For people who relapsed while receiving tailored infliximab, dose escalation was allowed. All patients in active disease could receive surgery or remain on second-line treatment until the end of the analysis.

The 1-year probability of clinical relapse in the no treatment group was estimated from a meta-analysis of placebo arms (Renna 2008) and varied in sensitivity analyses. The relative risk of relapse for metronidazole and azathioprine were obtained from pairwise meta-analyses reported in a Cochrane review (Doherty 2009). The relative risk of relapse for people receiving infliximab was assumed to be 0.01 as the authors considered a relapse rate of 0% reported in a small trial by Regueiro 2009 to be an underestimate. For the tailored infliximab strategy, the probability of endoscopic recurrence at 6 months was extracted from Rutgeerts 1990, which was a prospective cohort study that characterised the postoperative course of Crohn's disease in patients who were not receiving any treatment. The rate of reoperation was sourced from Wolters 2006, a cohort study conducted in a European population of patients with Crohn's disease. Health-state utilities were obtained from Lindsay 2008 an economic evaluation modelling the use of infliximab in patients with fistulising disease, which reported EQ-5D values of 0.83 for remission, 0.55 for clinical relapse and 0.4 for surgery.

The model captured the cost of drugs, reoperation and colonoscopy. Additionally, the monthly costs of remission and relapse were based on an analysis of Medicare and commercial claims data by Malone 2010. In the base case deterministic analysis, assuming a baseline probability of relapse of 24% at 1 year for the no treatment strategy, upfront infliximab was found to be the most effective strategy but was not cost-effective, ICER $2,719,014 (£2,065,005)/QALY at an author-defined willingness-to-pay threshold of $80,000 (£60,757) per QALY. Azathioprine, no treatment and tailored infliximab were dominated by metronidazole, meaning that metronidazole was both less costly and more effective. When the baseline probability of relapse was varied in sensitivity analyses (from a low of 0.10 to a high 0.78), metronidazole remained the most cost-effective strategy. The authors also explored the impact of increasing the time horizon of the model to 3 years; metronidazole remained the most cost-effective strategy. This study was found to be partially applicable

because not all treatments of interest to the review question for post-surgical maintenance of remission of Crohn's disease were compared and because the analysis was conducted from a US payer perspective where costs are likely to be different from the UK. This study was found to have potentially serious limitations because the time horizon was limited to 1 year and may not reflect all important differences in costs and outcomes between strategies. In addition, estimates of relative effectiveness for metronidazole and azathioprine were based on pairwise meta-analyses while the efficacy of infliximab was based on 1 small trial and subject to strong assumptions by the authors. No probabilistic sensitivity analysis was conducted.

Doherty 2012 conducted a cost-utility analysis to compare no treatment, mesalazine, azathioprine/mercaptopurine and infliximab as strategies for post-surgical maintenance of remission, adopting a US societal perspective. The analysis was constructed as a decision tree with a 1-year time horizon, given the available duration of follow-up from trials. Clinical relapses were assumed to be moderately severe in nature and were assumed to occur halfway through the year. People who relapsed were switched to the next agent in step-up therapy and remained on it for the duration of the analysis. The sequence of treatments used was mesalazine, azathioprine, infliximab and adalimumab. The efficacy of no treatment, mesalazine and azathioprine or mercaptopurine were taken from pairwise meta-analyses reported in a Cochrane review (Doherty 2009).

The efficacy of infliximab was extracted from Regueiro 2009 and the probability of infliximab-related adverse events was based on the ACCENT I study as reported in Hanauer 2002. Health-state utilities for clinical remission (0.88) and relapse (0.78) were taken from Gregor 1997, which were estimated from a cohort of 180 patients with Crohn's disease using standard gamble. The model took into account the costs of drugs, including administration costs, and the costs of treating subsequent relapses. The authors conducted an exploratory analysis with a 5-year time horizon in which they assumed clinical relapse would occur at 30 months after surgery; costs and utilities were discounted at a rate of 3% per year. The results of the 1-year analysis showed that compared to a no treatment strategy, none of the other drugs were cost effective at threshold values between $50,000 (£37,973) to $100,000 (£75,947) per QALY. A similar conclusion was drawn for the 5-year analysis. The authors also performed an exploratory analysis using endoscopic relapse (defined as a Rutgeerts score>i2) instead of clinical relapse. In this analysis, azathioprine was found to be cost effective compared to no treatment with an ICER of $7,552 (£5,736)/QALY.

Overall, this study was found to be partially applicable because not all treatments of interest to the review question for post-surgical maintenance of remission of Crohn's disease were compared and because the analysis was conducted from a US perspective where costs are likely to be different from the UK. This study was found to have potentially serious limitations because the structure of the decision tree required strong assumptions to be made about the timing of relapses that may not reflect the natural course of the disease. Estimates of relative effectiveness of treatments were based on pairwise meta-analyses while the effectiveness of infliximab was based on 1 small trial. Although an exploratory analysis was conducted to extend the time horizon to 5 years, it did not take into account other potentially relevant costs and outcomes such as the need for reoperation.

Table 1: Summary of economic evaluations included in the review

Study	Comparators	Costs[a]	Effects	ICER	Uncertainty	Applicability	Limitations
Ananthakrishnan 2011	Metronidazole	£2,113	0.821 QALY	-	Probabilistic sensitivity analysis was not undertaken. A number of scenario analyses were performed including varying the baseline rate of relapse, varying the relative treatment effects, varying health-state utilities, varying the treatment algorithm and extending the time horizon to 3 years. Metronidazole remains the preferred strategy across most scenarios. The QALY gains for infliximab are greater when the baseline risk of relapse is higher but the ICER remains in excess of the author-defined WTP threshold.	Partially applicable	Potentially serious limitations
	Azathioprine	£2,444	0.814 QALY	Dominated[b]			
	No treatment	£2,980	0.805 QALY	Dominated			
	Tailored infliximab	£6,099	0.821 QALY	Dominated			
	Upfront infliximab	£16,818	0.828 QALY	£2,065,005 /QALY			
Doherty 2012	No treatment	£1,486	0.840 QALY	Dominant	The no treatment strategy was associated with the highest net health benefit up to a threshold of $245,000 (£186,000)/QALY. The ICER for mesalazine vs. no treatment was <$50,000 (£37,206)/QALY when the baseline probability of relapse was increased to 66%. The ICER for azathioprine was <$50,000 (£37,206)/QALY when endoscopic relapse was modelled in an exploratory analysis.	Partially applicable	Potentially serious limitations
	Mesalazine	£4,484	0.850 QALY	Ext. dominated			
	Azathioprine/ mercaptopurine	£5,082	0.860 QALY	£179,804 /QALY			
	Infliximab	£19,083	0.870 QALY	£1,400,080 /QALY			

(a) Costs converted from 2010 US dollar using a conversion factor of 0.70 and an implied inflation factor of 1.08 (EPPI centre converter)
(b) A technology is said to be dominated when it is more costly and less effective than one or more other comparators.

Economic model

The 2 published economic evaluations included in the review only partially address the review question about treatments for post-surgical maintenance of remission in Crohn's disease. Neither study was conducted in a UK setting nor compared all drugs of relevance to the decision space. The base case analyses for both models were limited to a 1-year time horizon and used clinical relapse as the main outcome of interest. In order to take into account RCT evidence that has become available since the 2012 guideline, we undertook network meta-analyses and constructed a de novo economic model to address this review question. The remainder of this section provides a summary of the structure and main results of the economic model. A more comprehensive description of methods, results and sensitivity analyses can be found in Appendix L.

Population

Adults who have undergone complete macroscopic resection of ileocolonic Crohn's disease in the preceding 3 months.

Comparators

The economic model compares a no treatment strategy with 10 drugs or combinations of drugs for which RCTs were identified in the clinical review and reported the outcome endoscopic relapse (defined as a Rutgeerts' score ≥i2):

1. No treatment
2. Adalimumab
3. Azathioprine
4. Budesonide
5. Infliximab
6. Mercaptopurine
7. Mesalazine
8. Metronidazole
9. Infliximab + mesalazine (INF+MES)
10. Metronidazole + adalimumab (MET+ADA)
11. Metronidazole + azathioprine (MET+AZA)

A scenario analysis was conducted using clinical relapse as the main outcome in the economic model, for which comparative evidence on 1 additional drug, sulfasalazine, was available.

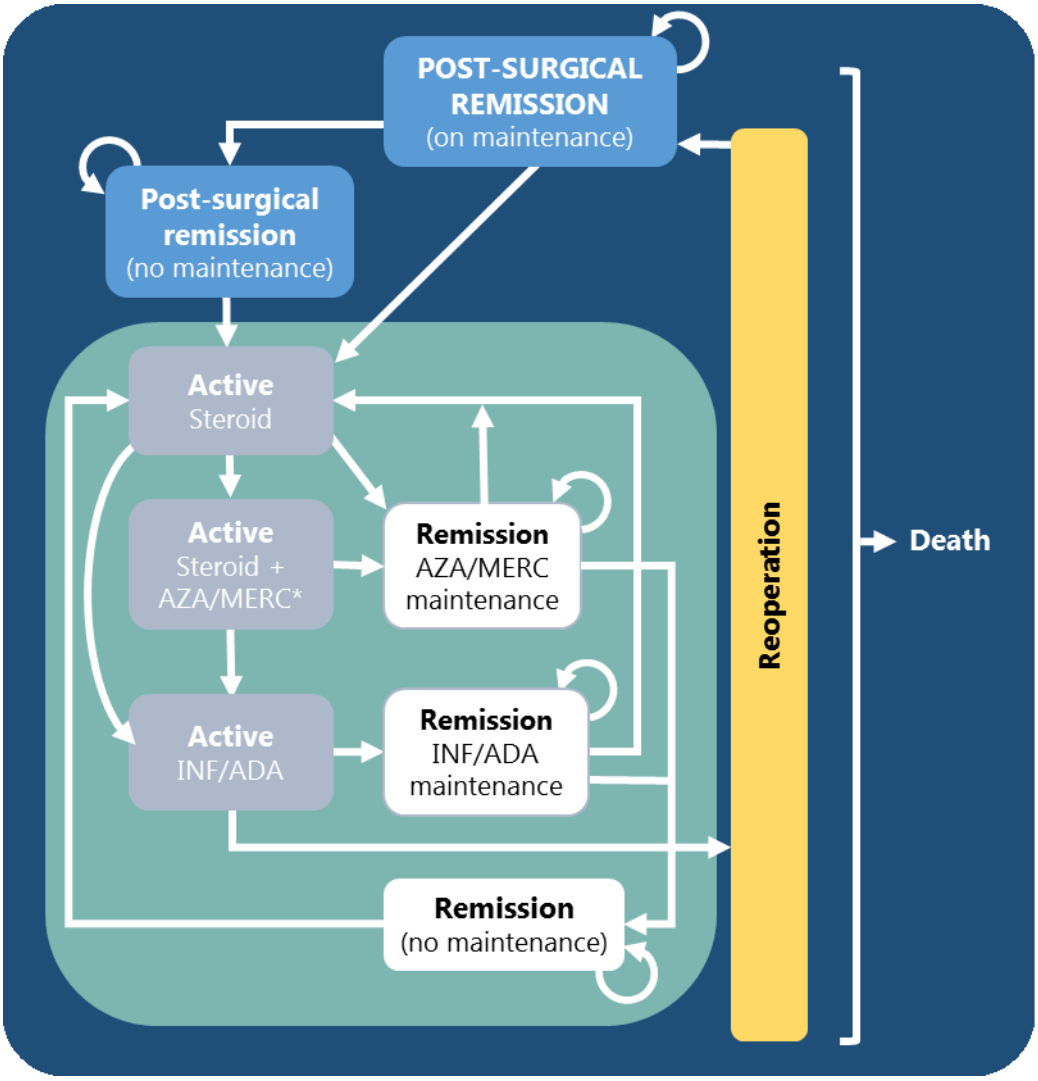
Methods

The model was constructed as a cost-utility analysis from a UK NHS/personal social services perspective with a 3-year time horizon. The time horizon was chosen because it reflected the longest duration of follow-up across a number of RCTs included in the evidence review. The committee was uncertain if the relative treatment effects reported in RCTs could be extrapolated beyond 3 years but also felt it was important for the model to consider the impact of downstream costs and health effects in people who relapsed while on treatment for post-surgical maintenance of remission. The impact of a longer time horizon was explored in scenario analyses. Costs were reported in GBP (£) and health outcomes reported as quality-adjusted life years (QALYs), both discounted at an annual rate of 3.5%.

Model structure

The model was developed using a Markov process with a 2-month cycle length to simulate the post-operative course of Crohn's disease. The overall structure of the model is shown in Figure 1.

Figure 1: Overall structure of the Markov model



The health states post-surgical remission (on maintenance) and remission INF/ADA maintenance were modelled as tunnel states. The green area highlights downstream events in the model informed by recommendations made elsewhere in the 2012 guideline for induction of remission and maintenance of medically-induced remission.AZA = azathioprine; MERC = mercaptopurine; INF = infliximab; ADA = adalimumab

The cohort is assumed to start in the post-surgical remission (on maintenance) state receiving one of the strategies listed above. From this initial state, people can remain in remission, withdraw from post-surgical maintenance treatment or experience disease relapse. For people who withdraw from post-surgical maintenance treatment, their disease is initially assumed to be in remission but they face a higher rate of relapse associated with no post-surgical maintenance treatment. People whose disease relapses while on post-surgical maintenance treatment are assumed to require further treatment to induce remission as described elsewhere in this guideline. In the first instance, people would receive a conventional glucocorticosteroid. If remission is achieved with a glucocorticosteroid, the model

assumes everyone will receive azathioprine or mercaptopurine as maintenance treatment. If remission is not achieved with a glucocorticosteroid, the model assumes azathioprine or mercaptopurine would be added to the glucocorticosteroid to induce remission. However, for people whose disease relapsed while receiving azathioprine or mercaptopurine as post-surgical treatment for maintenance of remission, it is unlikely that the same drug would be used again to induce remission so in a scenario analysis, it was assumed these people would receive methotrexate instead. People whose disease has not responded to immunosuppressive and/or glucocorticosteroid treatment are assumed to receive infliximab or adalimumab. People who respond to infliximab or adalimumab are assumed to remain on treatment for 12 months; people who do not respond to infliximab or adalimumab are assumed to undergo reoperation. In the base case, it was assumed that following reoperation, people would return to the same post-surgical maintenance strategy that they received at the start of the model.

Evidence from a matched cohort study of people with inflammatory bowel disease using the UK Clinical Practice Research Datalink cohort showed that Crohn's disease is associated with an increased risk of death (Chu 2017). This was incorporated in the economic model by applying the excess mortality risk for Crohn's disease to general population mortality rates from age-specific life tables for England and Wales (2015-17). It was assumed that the starting age of the cohort was 35 years. Differences in treatment-specific mortality rates were not modelled because this outcome was not reported in most of the trials that were included in the evidence review.

Baseline rate of relapse

The baseline rate of relapse for the no treatment strategy in the economic model was derived from a prospective cohort study (Rutgeerts 1990). This study characterised the natural course of disease recurrence in 89 people who were not receiving any treatment following ileal or ileocolonic resection for Crohn's disease. The study reported both endoscopic relapse (in years 1 and 3 following surgery) and clinical relapse (in years 1, 2 and 3 following surgery). The probabilities summarised in Table 2 reflect the number of relapses divided by the number at risk, assuming a constant rate within each time period in which relapses were reported. Consistent with the committee's experience, endoscopic relapse rates were higher than clinical relapse rates following surgery. The committee considered endoscopic relapse to be a more objective measure of disease that can impact treatment decisions in the absence of clinical symptoms. The committee agreed that over time, the goal of treatment in Crohn's disease has shifted from symptom relief to achieving or maintaining mucosal healing as this is associated with better long-term outcomes (Shah 2016). Therefore, greater emphasis was placed on the endoscopic relapse rates, which were used in the base-case analysis of the economic model.

Table 2: Baseline probability of relapse with no maintenance treatment following surgery for Crohn's disease

	Endoscopic relapse ≥i2	Clinical relapse
Year 1 Probability (SE)	60.3% (5.2%)	19.8% (4.2%)
Year 2 Probability (SE)	18.2% (4.1%)	12.0% (3.5%)
Year 3 Probability (SE)	18.2% (4.1%)	4.0% (2.1%)

Treatment effects

Network meta-analysis (NMA) was undertaken to estimate the relative effects of treatments for post-surgical maintenance of remission for the following outcomes:

withdrawal due to adverse events, endoscopic relapse and clinical relapse. More detailed descriptions of the methods and results of the NMAs are provided in Appendix I. Relative effects were estimated as log hazard ratios (assuming a binomial likelihood and cloglog link function) and combined with the baseline (log) rate of relapse from the Rutgeerts 1990 natural history study. The inverse cloglog transformation was used to generate 2-month transition probabilities in the economic model.

In adopting a cloglog model to estimate relative treatment effects, an assumption was made that the relapse rate across RCTs was constant over time and followed an exponential distribution. However, the relapse rates observed in the natural history study suggest this may not be the case. To assume anything other than an exponential distribution in the cloglog model would require relapse data to be reported at more than one time point in the same study. For endoscopic relapse, there was only 1 RCT (Savarino 2013) in the network that reported relapse events at more than 1 time point. Given the limited availability of data to reliably estimate a changing hazard over time, a decision was made to apply constant hazard ratios for relative effects estimated in the NMA to a changing baseline hazard informed by the natural history study in the economic model. It was also not possible to take account of the statistical dependency between withdrawal and endoscopic (or clinical) relapse and therefore they were analysed as independent outcomes. The base case cost-effectiveness analysis uses the data on endoscopic relapse with clinical relapse data considered in a scenario analyis.

In the economic model, probabilities for withdrawal due to adverse events and relapse were applied in a sequential manner. People withdrawing from post-surgical maintenance treatment were assumed to be in remission and transitioned to a separate health state for post-surgical remission (no maintenance) where they faced a rate of relapse associated with no treatment. The probability of relapse and remission were then applied to the remaining people in the post-surgical (on maintenance) health state who had not withdrawn from treatment.

The effectiveness of drugs for treating the downstream consequences of relapses were obtained from the evidence reviews and syntheses for induction of remission and maintenance of remission reported elsewhere in the 2012 Crohn's disease guideline.

Costs

There were 4 categories of costs included in the model:

1. **Drug costs** – acquisition costs of drugs to maintain or induce remission plus anyadministration costs
2. **Drug monitoring costs** – healthcare costs related to preliminary checks at start of therapy or therapeutic monitoring during active treatment
3. **Disease state costs** – resources associated with disease monitoring, appointments and hospital admissions in the active disease state and remission state
4. **Surgery costs** – cost of reoperation

Health-related quality of life

Health-state utilities reflecting active Crohn's disease and remission were sourced from Stark 2010. The study captured responses from 270 people with Crohn' disease using the EQ-5D questionnaire, which were valued using the UK tariff. It was not possible to identify suitable disutility values in the literature to apply to people withdrawing due to adverse events but this was explored in a scenario analysis.

Results

This section presents results of the base case cost-effectiveness analysis for endoscopic relapse, a scenario using clinical relapse data and further scenarios in which azathioprine and/or metronidazole are excluded from the model to reflect treatment options for people who are intolerant to one or both of these drugs. A number of additional scenario analyses are reported in Appendix M.

Endoscopic relapse

Table 3 shows the deterministic results for the base-case analysis using endoscopic relapse data and assuming a 3-year time horizon. A combination of metronidazole (given for 3 months) plus azathioprine was the most cost-effective strategy. All other strategies are dominated with exception of adalimumab. Adalimumab is the most effective strategy as it produces the most QALYs but the incremental cost-effectiveness ratio (ICER) for adalimumab in comparison to metronidazole plus azathioprine is well above £20,000/QALY.Table 4 shows the mean probabilistic results of 1,000 iterations for this scenario. The results show that the combination of metronidazole (given for 3 months) plus azathioprine has a 92.8% probability of being the most cost-effective strategy. This is graphically represented over a range of threshold values in the cost-effectiveness acceptability curve (CEAC) in **Figure 2**.

Table 3: Deterministic results for endoscopic relapse, 3-year time horizon

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£5,504	2.674			
Azathioprine	£6,684	2.658	£1,180	-0.016	dominated
Metronidazole[(a)]	£6,726	2.655	£1,222	-0.019	dominated
No treatment	£7,096	2.649	£1,591	-0.025	dominated
Mesalazine	£7,611	2.654	£2,107	-0.020	dominated
Budesonide	£7,984	2.649	£2,479	-0.025	dominated
Mercaptopurine	£8,595	2.669	£3,090	-0.005	dominated
MET+ADA[(a)]	£26,345	2.682	£20,840	0.008	ext. dom.
INF+MES	£27,456	2.670	£21,951	-0.004	dominated
Adalimumab	£28,465	2.699	£22,960	0.025	£922,416
Infliximab	£31,357	2.683	£2,892	-0.016	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Table 4: Mean probabilistic results for endoscopic relapse, 3-year time horizon

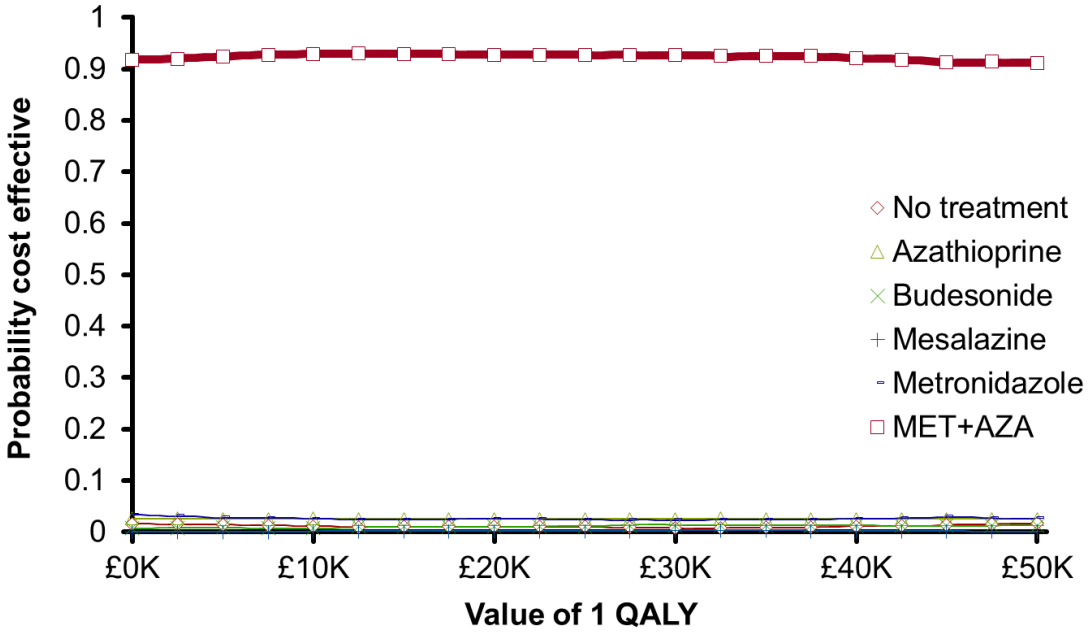
	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£5,592	2.655				92.8%
Azathioprine	£6,731	2.639	£1,139	-0.015	dominated	2.5%
Metronidazole[(a)]	£6,786	2.636	£1,194	-0.018	dominated	2.5%
No treatment	£7,135	2.631	£1,543	-0.024	dominated	1.0%
Mesalazine	£7,651	2.636	£2,059	-0.019	dominated	0.2%

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
Budesonide	£8,026	2.631	£2,433	-0.024	dominated	1.0%
Mercaptopurine	£8,626	2.651	£3,034	-0.004	dominated	0.0%
MET+ADA[(a)]	£25,830	2.660	£20,237	0.006	ext. dom.	0.0%
INF+MES	£27,190	2.651	£21,598	-0.004	dominated	0.0%
Adalimumab	£28,274	2.680	£22,682	0.025	£901,306	0.0%
Infliximab	£31,242	2.665	£2,968	-0.015	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months.

Figure 2: Cost-effectiveness acceptability curve for endoscopic relapse, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

Clinical relapse

Table 5: Deterministic results for clinical relapse, 3-year time horizon

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£3,974	2.697			
Metronidazole[(a)]	£4,371	2.689	£397	-0.008	dominated
No treatment	£4,470	2.684	£496	-0.013	dominated
Sulfasalazine	£4,511	2.690	£536	-0.006	dominated
Azathioprine	£4,660	2.687	£686	-0.010	dominated
Mesalazine	£5,631	2.688	£1,657	-0.009	dominated
Budesonide	£5,824	2.685	£1,850	-0.011	dominated
Mercaptopurine	£7,885	2.690	£3,911	-0.007	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
INF+MES	£26,162	2.686	£22,188	-0.011	dominated
Adalimumab	£28,851	2.705	£24,877	0.008	ext. dom.
MET+ADA[(a)]	£29,794	2.705	£25,820	0.009	£2,960,186
Infliximab	£32,344	2.692	£2,549	-0.013	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidzole administered for 3 months

Table 6 shows the deterministic results using clinical relapse data and assuming a 3-year time-horizon. The combination of metronidazole (for 3 months) and azathioprine dominates all other strategies except the combination of adalimumab with metronidazole (for 3 months). Table 6 shows the mean probabilistic results of 1,000 iterations for this scenario. The combination of metronidazole (for 3 months) and azathioprine has a 70.5% probability of being cost effective. Adalimumab in combination with metronidazole (for 3 months) is the most effective strategy but the ICER is well above £20,000/QALY. The CEAC is presented in **Figure 3**.

Table 5: Deterministic results for clinical relapse, 3-year time horizon

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£3,974	2.697			
Metronidazole[(a)]	£4,371	2.689	£397	-0.008	dominated
No treatment	£4,470	2.684	£496	-0.013	dominated
Sulfasalazine	£4,511	2.690	£536	-0.006	dominated
Azathioprine	£4,660	2.687	£686	-0.010	dominated
Mesalazine	£5,631	2.688	£1,657	-0.009	dominated
Budesonide	£5,824	2.685	£1,850	-0.011	dominated
Mercaptopurine	£7,885	2.690	£3,911	-0.007	dominated
INF+MES	£26,162	2.686	£22,188	-0.011	dominated
Adalimumab	£28,851	2.705	£24,877	0.008	ext. dom.
MET+ADA[(a)]	£29,794	2.705	£25,820	0.009	£2,960,186
Infliximab	£32,344	2.692	£2,549	-0.013	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(b) Metronidzole administered for 3 months

Table 6: Mean probabilistic results for clinical relapse, 3-year time horizon

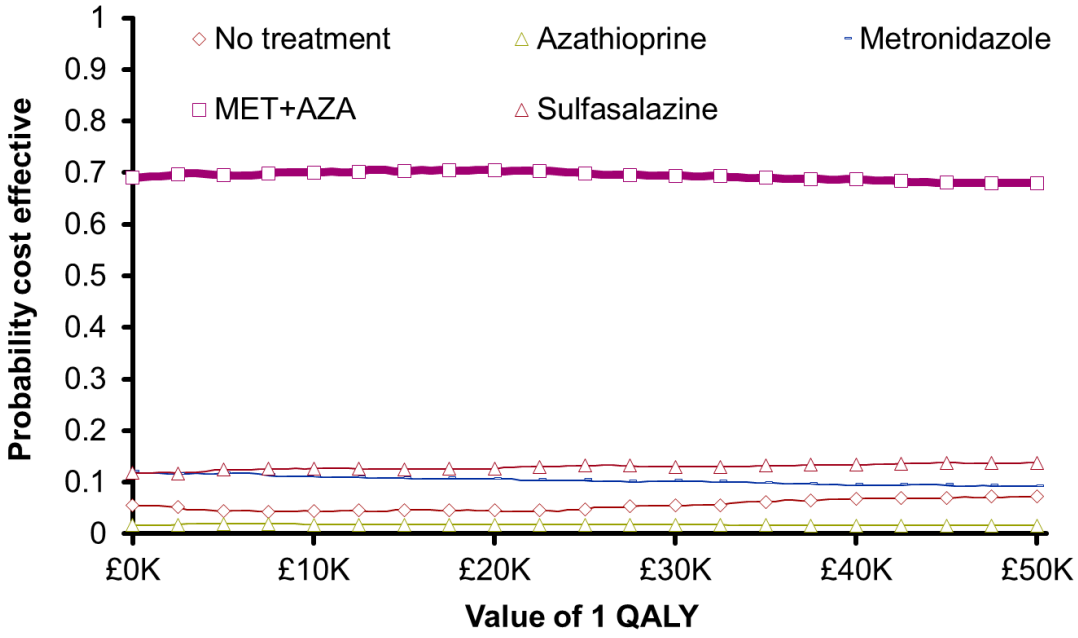
Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£4,123	2.699				70.5%
Metronidazole[(a)]	£4,485	2.691	£362	-0.007	dominated	10.6%
No treatment	£4,554	2.687	£431	-0.012	dominated	4.5%
Sulfasalazine	£4,601	2.694	£478	-0.005	dominated	12.6%
Azathioprine	£4,765	2.690	£642	-0.009	dominated	1.8%

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
Mesalazine	£5,700	2.691	£1,577	-0.008	dominated	0.0%
Budesonide	£5,946	2.688	£1,823	-0.011	dominated	0.0%
Mercaptopurine	£7,946	2.692	£3,823	-0.007	dominated	0.0%
INF+MES	£25,821	2.687	£21,698	-0.012	dominated	0.0%
Adalimumab	£28,774	2.709	£24,651	0.010	£2,406,637	0.0%
MET+ADA[(a)]	£29,607	2.709	£832	0.000	dominated	0.0%
Infliximab	£32,118	2.695	£3,344	-0.014	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months.

Figure 3: Cost-effectiveness acceptability curve for clinical relapse, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

No azathioprine

The committee highlighted that azathioprine intolerance can occur in 10-20% of adults in clinical practice and therefore a scenario analysis was run removing azathioprine from the decision space. This meant not only removing azathioprine as a treatment strategy for post-surgical maintenance of remission, but also removing it as a treatment strategy from downstream parts of the pathway. For second-line induction of remission, the model assumed methotrexate would be given in combination with glucocorticosteroids and for maintenance of medically-induced remission, it was assumed that people would receive mercaptopurine. Deterministic (Table 7) and probabilistic (Table 8) results are consistent, with metronidazole alone now having the highest probability of being cost effective (64.9%). Mercaptopurine and adalimumab strategies generate the most QALYs but with ICERs above £20,000/QALY. All other strategies are dominated. **Figure 5** shows the CEAC for this scenario.

Table 7: Deterministic results for endoscopic relapse with no azathioprine, 3-year time horizon

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Metronidazole[a]	£7,975	2.654			
No treatment	£8,584	2.648	£609	-0.006	dominated
Mesalazine	£8,939	2.653	£964	-0.001	dominated
Budesonide	£9,340	2.648	£1,365	-0.006	dominated
Mercaptopurine	£9,531	2.668	£1,556	0.014	£108,282
MET+ADA[a]	£26,985	2.682	£17,455	0.013	ext. dom.
INF+MES	£28,167	2.670	£18,636	0.001	dominated
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394
Infliximab	£31,935	2.683	£3,265	-0.016	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months.

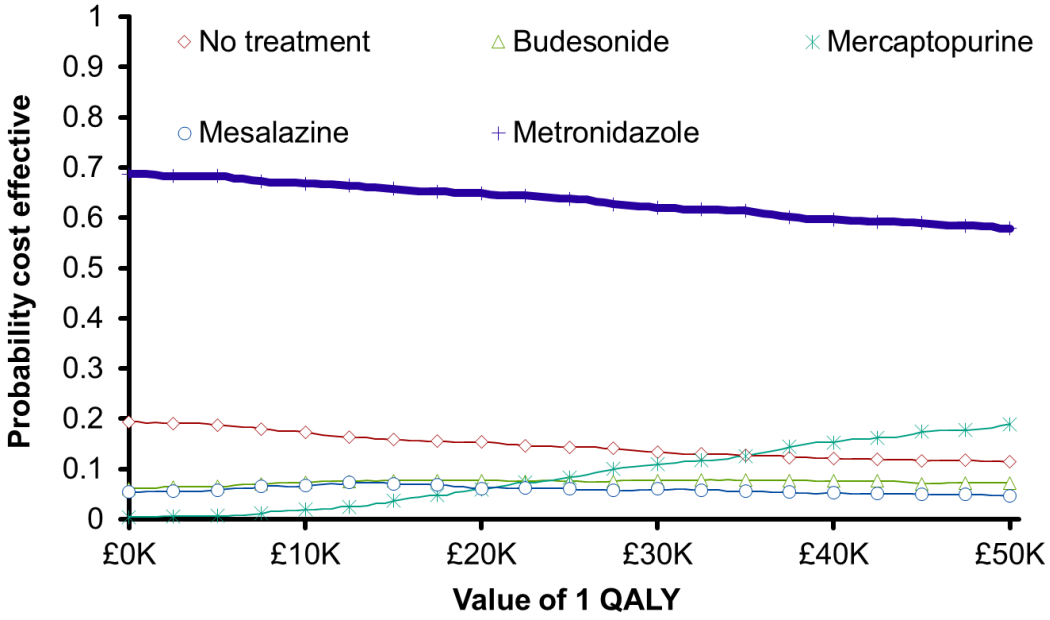
Table 8: Mean probabilistic results for endoscopic relapse with no azathioprine, 3-year time horizon

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
Metronidazole[a]	£8,104	2.662				64.9%
No treatment	£8,668	2.657	£564	-0.006	dominated	15.4%
Mesalazine	£9,024	2.662	£920	-0.001	dominated	6.1%
Budesonide	£9,434	2.657	£1,330	-0.006	dominated	7.7%
Mercaptopurine	£9,610	2.677	£1,506	0.015	£100,624	5.9%
MET+ADA[a]	£26,490	2.688	£16,881	0.011	ext. dom.	0.0%
INF+MES	£27,957	2.678	£18,347	0.001	dominated	0.0%
Adalimumab	£28,549	2.709	£18,939	0.032	£598,894	0.0%
Infliximab	£31,814	2.693	£3,266	-0.016	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months.

Figure 4: Cost-effectiveness acceptability curve for endoscopic relapse with no azathioprine, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

No azathioprine and no metronidazole

Similar to azathioprine, metronidazole may be poorly tolerated by some people. Two scenarios were implemented in which metronidazole was excluded from the model. In the first, all strategies including either azathioprine or metronidazole were excluded and in the second only strategies with metronidazole were removed.

For the first scenario, deterministic (Table 9) and probabilistic (

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
No treatment	£8,584	2.648			
Mesalazine	£8,939	2.653	£355	0.005	ext. dom.
Budesonide	£9,340	2.648	£757	0.000	dominated
Mercaptopurine	£9,531	2.668	£947	0.020	£46,637
INF+MES	£28,167	2.670	£18,636	0.001	ext. dom.
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394
Infliximab	£31,935	2.683	£3,265	-0.016	dominated
IINF+MES = infliximab in combination with mesalazine					

Table 10) results are consistent with no treatment now having the highest probability of being cost effective (50.5%). No treatment dominates all comparators except mercaptopurine and adalimumab but both of these options generate ICERs above £20,000/QALY. Figure 5 presents the CEAC for this scenario.

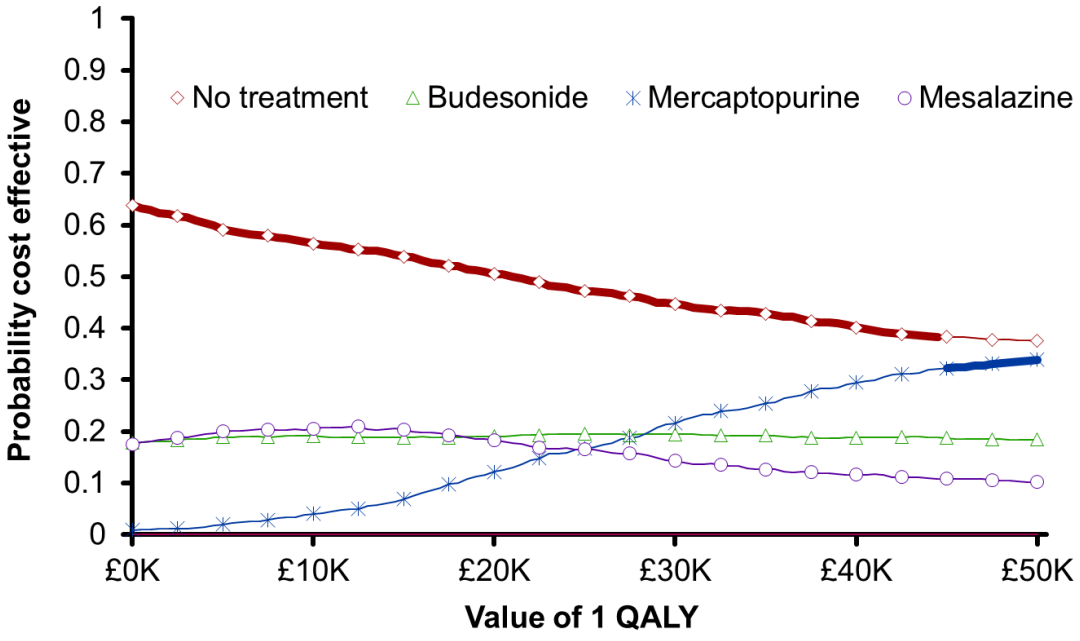
Table 9: Deterministic results for endoscopic relapse with no azathioprine and no metronidazole, 3-year time horizon

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
No treatment	£8,584	2.648			
Mesalazine	£8,939	2.653	£355	0.005	ext. dom.
Budesonide	£9,340	2.648	£757	0.000	dominated
Mercaptopurine	£9,531	2.668	£947	0.020	£46,637
INF+MES	£28,167	2.670	£18,636	0.001	ext. dom.
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394
Infliximab	£31,935	2.683	£3,265	-0.016	dominated
IINF+MES = infliximab in combination with mesalazine					

Table 10: Mean probabilistic results for endoscopic relapse with no azathioprine and no metronidazole, 3-year time horizon

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
No treatment	£8,704	2.639				50.5%
Mesalazine	£9,075	2.644	£371	0.005	ext. dom.	18.3%
Budesonide	£9,444	2.639	£741	0.000	dominated	19.0%
Mercaptopurine	£9,638	2.660	£935	0.021	£44,600	12.2%
INF+MES	£27,988	2.661	£18,350	0.001	ext. dom.	0.0%
Adalimumab	£28,526	2.691	£18,887	0.031	£600,073	0.0%
Infliximab	£31,853	2.675	£3,327	-0.016	dominated	0.0%
INF+MES = infliximab in combination with mesalazine						

Figure 5: Cost-effectiveness acceptability curve for endoscopic relapse with no azathioprine and no metronidazole, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

The deterministic results for the scenario with no metronidazole in the model are shown in Table 11. These are consistent with the probabilistic results (

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Azathioprine	£6,684	2.658			
No treatment	£7,096	2.649	£412	-0.009	dominated
Mesalazine	£7,611	2.654	£927	-0.004	dominated
Budesonide	£7,984	2.649	£1,300	-0.008	dominated
Mercaptopurine	£8,595	2.669	£1,910	0.011	£167,707
INF+MES	£27,456	2.670	£18,861	0.001	ext. dom.
Adalimumab	£28,465	2.699	£19,870	0.030	£665,175
Infliximab	£31,357	2.683	£2,892	-0.016	dominated
INF+MES = infliximab in combination with mesalazine					

Table 12) with azathioprine having the highest probability of being the most cost-effective strategy (72.0%) and dominating most strategies except mercaptopurine and adalimumab, which generate ICERs in excess of £20,000/QALY. The CEAC for this scenario is shown in Figure 6.

Table 11: Deterministic results for endoscopic relapse with no metronidazole, 3-year time horizon

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Azathioprine	£6,684	2.658			
No treatment	£7,096	2.649	£412	-0.009	dominated
Mesalazine	£7,611	2.654	£927	-0.004	dominated
Budesonide	£7,984	2.649	£1,300	-0.008	dominated
Mercaptopurine	£8,595	2.669	£1,910	0.011	£167,707
INF+MES	£27,456	2.670	£18,861	0.001	ext. dom.
Adalimumab	£28,465	2.699	£19,870	0.030	£665,175
Infliximab	£31,357	2.683	£2,892	-0.016	dominated
INF+MES = infliximab in combination with mesalazine					

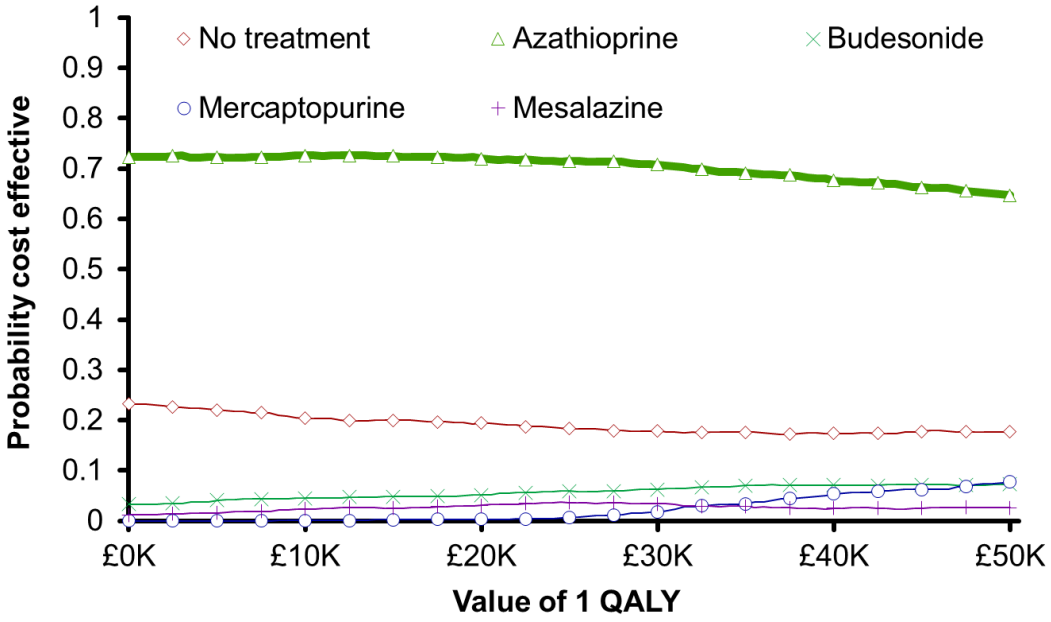
Table 12: Mean probabilistic results for endoscopic relapse with no metronidazole, 3-year time horizon

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
Azathioprine	£6,779	2.643				72.0%
No treatment	£7,155	2.635	£376	-0.008	dominated	19.5%
Mesalazine	£7,674	2.640	£895	-0.003	dominated	3.1%
Budesonide	£7,992	2.636	£1,213	-0.007	dominated	5.1%
Mercaptopurine	£8,644	2.654	£1,865	0.011	£167,993	0.3%
INF+MES	£27,171	2.655	£18,527	0.001	ext. dom.	0.0%
Adalimumab	£28,288	2.684	£19,643	0.029	£673,636	0.0%

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
Infliximab	£31,242	2.669	£2,955	-0.014	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

Figure 6: Cost-effectiveness acceptability curve for endoscopic relapse with no metronidazole in the model, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

No azathioprine, no metronidazole and no mesalazine

There was some uncertainty about the clinical benefit of mesalazine for maintaining endoscopic remission in the NMA. In this scenario, ICERs were recalculated after removing azathioprine, metronidazole and mesalazine from the decision space. The deterministic and probabilistic results are shown in Table 13 and Table 14. No treatment now has the highest probability of being cost effective (59.4%) and dominates all strategies except mercaptopurine and adalimumab. However, the ICERs for both of these strategies are above £20,000/QALY. The CEAC for this scenario is shown in Figure 7.

It was noted that the cost per pack of mercaptopurine had more than doubled since the 2012 guideline. Therefore, an exploratory analysis was run to estimate the cost at which mercaptopurine would become cost effective assuming a threshold of £20,000/QALY. This analysis found that the ICER for mercaptopurine compared to no treatment would fall to £20,000/QALY at a cost of £36.67 per pack (£3.93 per

day), which represents a 25% discount to the current list price of £49.15 per pack (£2.93 per day).

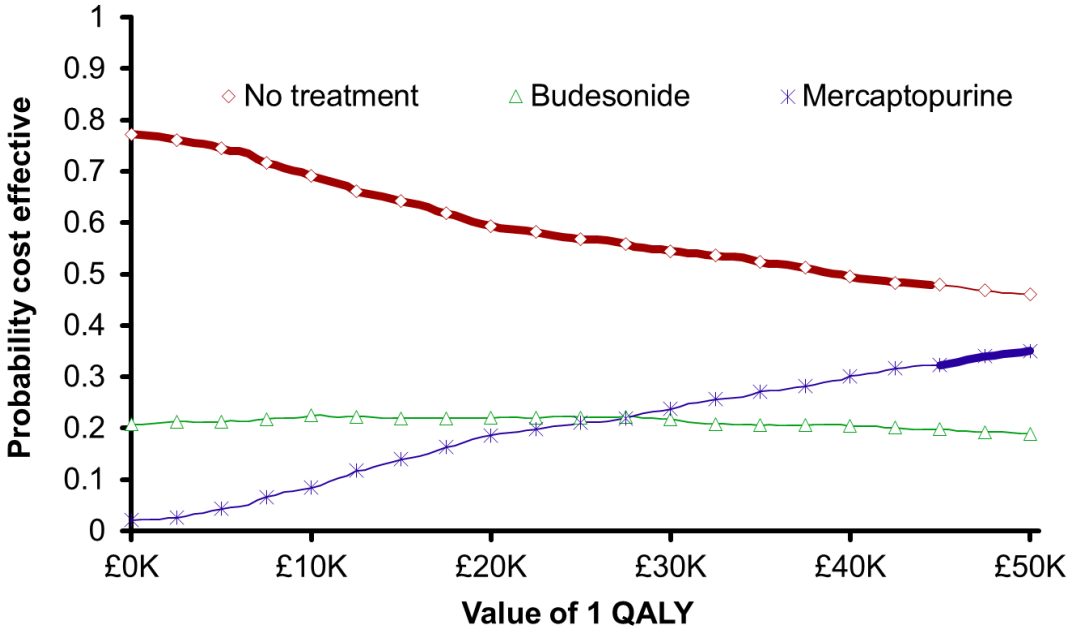
Table 13: Deterministic results for endoscopic relapse with no azathioprine, no metronidazole and no mesalazine, 3-year time horizon

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
No treatment	£8,584	2.648			
Budesonide	£9,340	2.648	£757	0.000	ext. dom.
Mercaptopurine	£9,531	2.668	£947	0.020	£46,637
INF+MES	£28,167	2.670	£18,636	0.001	ext. dom.
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394
Infliximab	£31,935	2.683	£3,265	-0.016	dominated
INF+MES = infliximab in combination with mesalazine					

Table 14: Probabilistic results for endoscopic relapse with no azathioprine, no metronidazole and no mesalazine, 3-year time horizon

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
No treatment	£8,655	2.651				59.4%
Budesonide	£9,371	2.653	£717	0.002	ext. dom.	22.0%
Mercaptopurine	£9,583	2.672	£928	0.021	£44,830	18.6%
INF+MES	£27,938	2.672	£18,356	0.000	ext. dom.	0.0%
Adalimumab	£28,507	2.701	£18,924	0.030	£639,540	0.0%
Infliximab	£31,851	2.686	£3,344	-0.015	dominated	0.0%
INF+MES = infliximab in combination with mesalazine;						

Figure 7: Cost-effectiveness acceptability curve for endoscopic relapse with no azathioprine, no metronidazole and no mesalazine, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

Evidence statements

Clinical evidence statements

Clinical relapse

Moderate quality evidence from 1 network-meta-analysis with 21 RCTs containing 2401 participants found that the following treatments were effective in reducing clinical relapse rates compared to placebo:

- Adalimumab
- Metronidazole (3 months) with adalimumab

Of these treatments, there were no difference in clinical relapse rates between them.

Endoscopic relapse

Moderate quality evidence from 1 network-meta-analysis with 16 RCTs containing 1586 participants found the following treatments were effective in reducing endoscopic relapse rates compared to placebo:

- Adalimumab,
- Infliximab,
- Mercaptopurine
- Infliximab with mesalazine.
- Metronidazole (3 months) with azathioprine

Of the treatments showing benefit over placebo or no treatment, the following were effective in reducing endoscopic relapse:

- Adalimumab, compared to mercaptopurine.
- Adalimumab, compared with infliximab.
- Adalimumab, compared with metronidazole (3 months) with azathioprine
- Infliximab with mesalazine, compared to mercaptopurine.
- Infliximab, compared to mercaptopurine.

The evidence could not differentiate endoscopic relapse rates between:

- Adalimumab, compared with infliximab with mesalazine,
- infliximab, compared with infliximab with mesalazine,
- and metronidazole (3 months) with azathioprine, compared to:
    - Infliximab,
    - Mercaptopurine and
    - Infliximab with mesalazine.

Withdrawal due to adverse events

High quality evidence from 1 network-meta-analysis with 17 RCTs containing 1922 participants found that no treatment was effective in reducing withdrawal due to adverse events compared to placebo or no treatment. One treatment, azathioprine, showed higher withdrawals due to adverse events compared to placebo.

Economic evidence statements

One partially applicable cost-utility analysis with potentially serious limitations (Ananthakrishnan 2011) compared no treatment, azathioprine, metronidazole, mercaptopurine and 2 infliximab strategies for post-surgical maintenance of clinical remission of Crohn's disease and concluded that metronidazole was the most cost-effective strategy.

One partially applicable cost-utility analysis with potentially serious limitations (Doherty 2012) compared 4 treatment strategies for post-surgical maintenance of clinical remission of Crohn's disease: no treatment, mesalazine, azathioprine/mercaptopurine and infliximab. The no treatment strategy was associated with the highest net health benefit up to a threshold of $245,000 (£186,000)/QALY.

One directly applicable original economic model with minor limitations compared 12 treatment strategies for post-surgical maintenance of endoscopic remission of Crohn's disease and found that the combination of metronidazole (for 3 months) plus azathioprine has the highest probability (93%) of being cost effective.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee considered all outcomes and there was sufficient evidence to conduct network meta-analysis on three outcomes: clinical relapse, endoscopic relapse and withdrawal due to adverse events. In the network meta-analysis, it was necessary to model outcomes as relapses rather than remission, as event data (the number of relapses occurring) was required in the network-meta-analysis. However, the committee were also interested in the primary outcome of clinical remission, as specified in the protocol, and this was presented in pairwise analysis. The committee noted that there is varying practice across the UK in how clinical relapse is assessed as it is a subjective measure. The committee agreed that endoscopic relapse, as assessed using the Rutgeerts' score, is a robust and objective measure and can provide a reliable indication of disease status in those with clinical symptoms or prior to symptoms occurring.

The quality of the evidence

The committee noted that many studies included were open-label or single-blinded trials, where there is a high risk of bias, in particular for the subjective outcome clinical relapse. Restricting the analysis for clinical relapse to double-blinded trials would have resulted in the loss of many treatment comparisons in the network-meta analysis. The committee noted that blinding is less of a concern for endoscopic relapse and that this is a more robust outcome on which to base recommendations.

The committee noted the limitations of the evidence included in the network meta-analysis for clinical relapse as defined by the author, namely that different methods of assessment were used. The committee specified that a sensitivity analysis including only studies that use the Crohn's Disease Activity Index (CDAI) as an outcome would be useful - where a score of 150 or below indicates clinical remission and above 150 indicates clinical relapse. However, the evidence from trials using a CDAI score >150 could not be connected or assessed in a network meta-analysis. The committee took

into account the network meta-analysis for withdrawals due to adverse events, but noted the limitations with this as adverse events are not well defined in the trials included. The committee noted it is unclear if disease worsening or disease progression are considered as adverse events in many of the trials and the adverse events reported may capture additional features not attributed to treatment side effects. This may be a reason why the network meta-analysis on adverse events did not show any clear differences among treatments in terms of the rate of withdrawals due to adverse events.

Benefits and harms

Evidence was available from the network meta-analysis to suggest that adalimumab is effective in reducing endoscopic and clinical relapse. The evidence suggesting this came from one small randomised controlled trial (Savarino 2013) which showed a large benefit of adalimumab over either azathioprine or mesalazine. When considered in the network meta-analysis, the large benefit to adalimumab contributed to uncertainty in the network around the benefit of either adalimumab, azathioprine or infliximab. The committee noted the limited clinical evidence available for infliximab and adalimumab, the uncertainty surrounding this and the cost considerations with initiating infliximab and adalimumab as maintenance therapy after surgery. Taking into account these considerations, the committee recommended to not start biologics to maintain remission after surgery. The committee agreed that if people are already taking biologics after surgery, they can continue with their current treatment until both they and their NHS healthcare professional agree it is appropriate to change.

The committee considered the evidence in relation to immunodulators. There is some evidence that azathioprine alone has a clinical benefit in reducing endoscopic relapse, but the evidence showed some uncertainty around this beneficial effect. The evidence found a clinical benefit for azathioprine with up to 3 months postoperative metronidazole, in particular for reducing endoscopic relapse. However, the committee noted that there is varying practice across the UK, as some people may not receive up to 3 months postoperative metronidazole. Metronidazole may be poorly tolerated, in which case azathioprine alone may be considered. The committee also estimated that 10-20% of adults may not be able to tolerate azathioprine. For these people, the committee did not wish to recommend metronidazole alone because they felt that the benefits of metronidazole given alone as a maintenance treatment after surgery did not outweigh the potential adverse effects. The committee also did not wish to recommend mesalazine because of the uncertainty surrounding the clinical benefit, particularly for the outcome endoscopic relapse. The committee discussed mercaptopurine as an alternative for people who cannot tolerate azathioprine. Azathioprine is a prodrug, which is converted to mercaptopurine in the body. However at the current list price, mercaptopurine was not cost effective. Due to concerns regarding tolerability and potential adverse effects, the committee decided to make a recommendation to monitor the effects of azathioprine and metronidazole, including monitoring neutropenia levels in those taking azathioprine.

The evidence assessed in the network meta-analysis found that budesonide was the least effective treatment in reducing endoscopic or clinical relapse. The committee noted that this is consistent with clinical practice and that budesonide would not normally be considered as a treatment option to maintain remission post-surgery. The committee recommended not offering budesonide to maintain remission after surgery. The committee noted that there was limited evidence on aminosalicylates alone and the evidence available does not show a benefit to mesalazine alone in reducing clinical or endoscopic relapse, or for sulfasalazine in reducing clinical relapse. The committee felt that a recommendation on aminosalicylates could not be

formulated given the limited evidence available and the lack of its use in clinical practice for the maintenance of remission after surgery.

No evidence on enteral nutrition from randomised controlled trials was found in this guideline update. The committee noted that this is an important area of research, as enteral nutrition alone or with other maintenance therapy is considered in clinical practice, particularly in infants and children. The committee made a recommendation for research for a randomised controlled trial focusing on the clinical and cost-effectiveness of enteral nutrition in maintaining remission after surgery.

Despite finding no paediatric evidence, the committee generalised the recommendations made to all people. The committee noted the treatments they have recommended do not have a UK market authorisation for the maintenance of remission after complete macroscopic resection. However, it was agreed that azathioprine with or without metronidazole is commonly used and, in their experience, management would be the same irrespective of age. The committee noted that the majority of evidence for this review question was from populations with macroscopic disease who have undergone ileocolonic resection, but did not stratify results by type of surgery performed. The committee stated that the management of Crohn's disease after surgery would be dependent on factors such as the location of the disease present and type of surgery performed and that the presence of any residual active disease could affect the balance of benefits and harms with respect to maintenance treatment. The committee emphasised that the evidence base and recommendations only apply to people starting treatment to maintain remission within 3 months of their complete macroscopic resection of ileocolonic Crohn's disease. The committee also emphasised that the recommendations apply to people with no residual active disease after surgery, as the management of this population would be different.

Cost effectiveness and resource use

A search of the published literature identified 2 partially applicable cost-utility analyses that each compared a subset of the drugs of relevance to the review question. Both of these published studies were conducted in the context of the US healthcare system, focussed on clinical relapse data and adopted a 1-year time horizon, reflecting the limited follow-up data that were available from randomised controlled trials at the time. Therefore, the committee felt it was important to undertake an original economic analysis to address these limitations.

The results of the original economic model showed that in the base-case endoscopic relapse analysis, the combination of metronidazole given for 3 months and azathioprine was the most cost-effective strategy. The committee noted that the differences in quality-adjusted life years (QALYs) between treatment strategies were generally small while the differences in costs between treatment strategies ranged from approximately £1,200 to more than £22,000. The results reflect the nature of maintenance treatment in which the entire cohort starts off in a state of remission receiving continuous treatment until withdrawal or relapse; maintenance treatment has not been shown to have a direct impact on Crohn's disease-related mortality and therefore in the model, the QALY differences between treatments are mainly driven by the difference in health status for people whose disease is active or in remission and by the relative proportions of people in these states over the time frame of the analysis. The committee felt that 3 years was the most appropriate time frame for the base-case analysis because this reflected the longest duration of follow-up that was available across several trials. They were uncertain if adherence to treatment and the relative effectiveness of treatments could be assumed to remain constant beyond this period. However, there was also recognition that the downstream costs and benefits

of maintenance treatment could extend beyond 3 years if more effective treatments continue to delay disease relapse and the need for further treatment and reoperation. Scenario analyses were conducted to explore a 10-year and a lifetime time horizon but did not result in any changes to the overall conclusions.

Additional scenario analyses were run for people who cannot tolerate azathioprine and/or metronidazole. The exclusion of azathioprine alone led to metronidazole (for 3 months) becoming the most cost-effective strategy. When metronidazole alone was excluded from the analysis, azathioprine had the highest probability of being cost effective. When both azathioprine and metronidazole were removed from the decision space, mesalazine had the highest probability of being cost effective but the QALY differences in comparison to no treatment were very small and the committee felt there was not enough evidence of its clinical effectiveness to recommend it.As the committee did not wish to recommend either metronidazole alone or mesalazine, the ICER for mercaptopurine versus no treatment was estimated and found to be just under £47,000/QALY. However, it was noted that the cost of mercaptopurine had increased since the 2012 guideline; if the drug were to be available at a discount of 25% or more to the current list price assumed in the analysis, then mercaptopurine is likely to be cost effective.

In the economic model, people who experienced relapse while on maintenance treatment were assumed to receive further treatment to induce remission in accordance with recommendations made elsewhere in this guideline. This includes step-up treatment with conventional glucocorticosteroids in the first instance followed by the addition of azathioprine or mercaptopurine if remission is not achieved and then a tumour necrosis factor (TNF) inhibitor (infliximab or adalimumab) and finally reoperation. The committee noted that in clinical practice, a number of other treatment options would be considered before reoperation, including dose escalation or switching between TNF inhibitors and other biologic therapies (vedolizumab and ustekinumab). However, there was uncertainty about the optimal strategy and consistency in clinical practice with respect to these options so they were not explicitly modelled as part of the downstream pathway. It was acknowledged that these additional options could further delay the need for reoperation and incur high costs but that the proportion of people affected in the model would be small and unlikely to change the conclusions of the analysis.

Finally, the committee noted the high drug costs for infliximab and adalimumab in the base case model and felt that these do not necessarily reflect locally negotiated prices. In addition the committee was aware that the patent for adalimumab was due to expire in October 2018, potentially leading to the availability of less expensive biosimilars. We explored the impact of reducing the cost per dose for both drugs by 25%, 50% and 75% and found that this did not change the overall conclusions. At a discount of 75%, infliximab remained dominated and the ICER for adalimumab vs. AZA+MET was approximately £200,000/QALY.

The committee discussed the likely resource impact of their recommendations. The use of azathioprine to maintain remission after surgery for Crohn's disease is in line with current clinical practice. They noted that biologics such as infliximab and adalimumab are sometimes used in the post-surgical maintenance setting but that this practice may not be consistent. Given limited resources, the recommendation not to recommend biologics to maintain remission after surgery could potentially result in cost savings by reducing the use of relatively high cost drugs and by improving consistency in clinical practice among people who have no residual active disease following ileocolonic resection.

Other factors the committee took into account

The committee discussed equalities issues and noted that there were no equalities considerations specific to people who have had surgery for Crohn's disease to take into account.

Appendices

Appendix A: Review protocol

Review protocol for post-surgical maintenance of remission

ID	Field (based on PRISMA-P)	Content
I	Review question	In adults and children what is the clinical and cost effectiveness of medical and/or nutritional treatment for post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer?
II	Type of review question	Intervention review
III	Objective of the review	To update and expand the question in the 2012 guideline. To assess the clinical and cost effectiveness of medical and/or nutritional treatment for post-surgical (commencing within three months of any intestinal surgery for Crohn's disease) maintenance of remission for 12 months or longer?
IV	Eligibility criteria – population	Patients of all ages who have had intestinal surgery within the last three months for active Crohn's disease.
V	Interventions	Post-surgical medical and/or enteral nutritional treatment: Oral budesonide Oral 5-aminosalicylates Oral Azathioprine/mercaptopurine Methotrexate Metronidazole Mycophenolate

ID	Field (based on PRISMA-P)	Content
		Enteral nutrition Infliximab,adalimumab and biosimilars Vedolizumab and Ustekinemab
VI	Comparator	No treatment Placebo Each other Combinations of drugs
VII	Outcomes	Maintenance of remission (for 12 months or longer) as defined by: Absence of clinical symptoms (determined by investigator) Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy Harvey Bradshaw Index (HBI) < 3 Endoscopic evaluation (Rutgeerts' score <i2) Faecal calprotectin Serious adverse events Infection Poor wound healing Withdrawal due to adverse events Readmission/hospitalisation Quality of life (including short QOL questionnaire, IMPACT 3 and IBS specific tools)
VIII	Eligibility criteria – study design	RCTs Systematic reviews of RCTs

ID	Field (based on PRISMA-P)	Content
IX	Other exclusion criteria	Follow up less than 12 months Non English- language papers Protocols, abstracts, conference proceedings, theses, non-peer reviewed publications
X	Proposed sensitivity/sub-group analysis, or meta-regression	If there is heterogeneity the following subgroups will be analysed separately: Montreal classification (Paris classification in children) Children, young people, adults Number of previous intestinal surgeries Preoperative medication Following formation of a stoma
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
XII	Data management (software)	See Appendix B
XIII	Information sources – databases and dates	See appendix C of the relevant chapter. An aligned search (Ulcerative colitis and Crohn's update) will be conducted from March 2012 (previous search date).
XIV	Identify if an update	Update of 2012 guideline question "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?"

ID	Field (based on PRISMA-P)	Content
XV	Author contacts	Guideline updates team
XVI	Highlight if amendment to previous protocol	This is a new protocol to reflect changes in the range of therapeutics available for this indication.
XVII	Search strategy – for one database	For details please see appendix C
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables). 10% of the data extraction were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix F (clinical evidence tables) or K (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B
XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B

ID	Field (based on PRISMA-P)	Content
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
XXIV	Assessment of confidence in cumulative evidence	See Appendix B
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the evidence review. The committee is convened by the NICE Guideline Updates Team and chaired by Tessa Lewis in line with section 3 of Developing NICE guidelines: the manual (2014).

ID	Field (based on PRISMA-P)	Content
		Staff from NICE will undertake systematic literature searches, appraise the evidence, conducd meta-analysis and cost-effectiveness analysis where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual (2014).
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

Appendix B: Methods and processes

Evidence synthesis and meta-analysis

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Quality assessment

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines' (2014). Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Methods for combining intervention evidence – pairwise analysis

Meta-analysis of interventional data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

No continuous outcomes were included in this guideline update. Dichotomous outcomes specified in the review protocol were pooled on the relative risk scale (using the Mantel–Haenszel method). Fixed effect and random effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed effect models were the preferred choice to report, but in situations where the assumption of a shared mean for Fixed effect model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random effects results are presented. Fixed effect models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

random effectsMeta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

For relative risks where no other MID was available, a GRADE default MID interval for relative risks of 0.8 to 1.25 was used. For hazard ratios where no other MID was available, the committee agreed that the line of no effect should be used to assess meaningful differences.

GRADE for pairwise meta-analyses of interventional evidence

Grading of Recommendations Assessment Development and Evaluation (GRADE) was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 15. No studies were included which had indirectness in terms of population, intervention or outcomes. Therefore, there were no serious indirectness in all outcomes.

Table 15: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

General methods

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally coherent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following two criteria were met:

- At least three treatment alternatives.
- A connected network to enable valid estimates to be made.

Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS cloglog model code provided in the appendices of TSD 2 was used to specify synthesis models. Additional code was added to account for missing data (Turner 2015).

Results were reported summarising 80,000 samples from the posterior distribution of each model, having first run and discarded 20,000 ‘burn-in’ iterations (convergence was then checked by visual inspection of trace and BGR plots). A few models required 30,000 burn in iterations. Two separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal(0,10000) priors, and the between-trial standard deviations used in random effects models were given Uniform(0,5) priors. The selected priors were sufficiently wide on a log hazard ratio scale.

A binomial likelihood and cloglog link model was fitted for all outcomes assessed. To account for the different length of follow-up in each trial, an underlying proportional hazards assumption was made with time to relapse following either an exponential or Weibull distribution. The assumptions made in this model are, namely, that the hazard ratios are constant over the entire duration of follow-up. This implies homogeneity of the hazard across people with Crohn’s disease in each trial.

Model selection

Fixed- and random effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random effects model, it was preferred; otherwise, the fixed effects model the fixed effect model provided a more parsimonious analysis, and was preferred. The goodness-of-fit of each model was assessed using the total residual deviance. This value was compared against the total number of data points (each study arm contributes 1 data point) to check if the model fit can be improved. Due to skewness identified in the distribution, the median values of the residual deviance was used when assessing goodness of fit and median hazard ratios were reported for the outcomes assessed.

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 16: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias[a]	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for a random effects model was lower than the DIC for a fixed-effect model.
Imprecision[b]	The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or statistical significance if MIDs were not available.

[a] Blinding was considered an important factor in assessing risk of bias for subjective outcomes, such as clinical remission/relapse. Double-blinded trials were considered at low-risk of bias for these outcomes, while single-blinded trials where the participants were not blinded or un-blinded trials were considered at high risk of bias. This is because performance bias can be introduced, where knowledge of which intervention was received biases outcome assessment by the trial co-ordinators or outcome reporting by the participant. For objective

GRADE criteria	Reasons for downgrading quality
outcomes, such as endoscopic remission/relapse, single-blinding or un-blinded trials were considered at moderate risk of bias, due to less chance of performance bias.	

[b] Cloglog link models used in the NMAs produce hazard ratios. As no MIDs for hazard ratios (HRs) were agreed by the committee and no default MIDs are available, the line of no effect (HR = 1) was used to asses meaningful differences in HRs in the outcomes assessed by NMAs.

Outcome selection

Using a binomial likelihood and cloglog link model assumes that a proportion of participants in all RCTs included reach an event after a period of follow-up. As remission is the absence of a relapse event, remission could not be directly modelled as the outcome in the network meta-analysis. The number of people experiencing disease relapse was extracted or derived for each arm of the RCTs. For all outcomes, the intention to treat (ITT) or modified intention to treat (mITT) population was used, where outcomes were reported for all participants who initiated treatment. RCTs with a minimum of 1-year follow-up were included. The hazard ratios were assumed to be constant across time and assumptions behind double counting depended on when withdrawals or losses to follow-up were reported (usually at the end of the study only. Therefore, the last follow-up time reported per outcome was included in the NMA. Three outcomes were assessed:

- Endoscopic relapse defined as a Rutgeerts' score of ≥i2

- Clinical relapse (author defined)

- Withdrawal due to adverse events

See Appendix I:Accounting for missing data for relapse outcomes for more detail on how missing data was accounted for.

Sensitivity analysis

The committee agreed to include all methods of assessing clinical relapse in the network-meta-analysis. It was noted that while the method of assessing clinical relapse varies in clinical practice, the most commonly used score is the Crohn's Disease Activity Index (CDAI), where a score of 150 or more indicates clinical relapse. This sensitivity analysis was specified due to its relevance to clinical practice. However, it was not possible to connect the network in the NMA to perform this sensitivity analysis due to insufficient data.

Where inconsistency was identified in the network, a sensitivity analysis was undertaken to remove studies contributing to inconsistency.

Appendix C: Literature search strategies

C.1 Search History

Databases	Date searched	Version/files	No. retrieved	EndNote data (post de-dupe)
Cochrane Central Register of Controlled Trials (CENTRAL)	02/11/2017	Issue 10 of 12, October 2017	1025	758
Cochrane Database of Systematic Reviews (CDSR)	02/11/2017	Issue 11 of 12, November 2017	65	30
Database of Abstracts of Reviews of Effect (DARE)	02/11/2017	Issue 2 of 4, April 2015	62	11
Health Technology Assessment (HTA Database)	02/11/2017	Issue 4 of 4, October 2016	30	15
Embase (Ovid)	02/11/2017	1974 to 2017 Week 44	8906	6032
MEDLINE (Ovid)	02/11/2017	1946 to October Week 4 2017	3230	2544
MEDLINE In-Process (Ovid)	02/11/2017	November 01, 2017	303	269

Additional search

Additional sets for Crohns part of the search (bold are extensions of lines already searched)

Vedolizumab/ [emtree only]

(Vedolizumab or Entyvio).tw.

Ustekinumab/ [MeSH and emtree]

(Ustekinumab or "cnto 1275" or cnto-1275 or stelara).tw

(infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab).tw

(Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa).tw.

Mycophenolic Acid/ (MeSH) mycophenolic acid/ (Emtree)

(Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw

Databases	Date searched	Version/files	No. retrieved	EndNote data (post de-dupe)
Cochrane Central Register of Controlled Trials (CENTRAL)	19/03/2018	Issue 2 of 12, February 2018	239	135

Databases	Date searched	Version/files	No. retrieved	EndNote data (post de-dupe)
Cochrane Database of Systematic Reviews (CDSR)	19/03/2018	Issue 3 of 12, March 2018	17	4
Database of Abstracts of Reviews of Effect (DARE)	19/03/2018	Issue 2 of 4, April 2015	1	0
Health Technology Assessment (HTA Database)	19/03/2018	Issue 4 of 4, October 2016	3	3
Embase (Ovid)	19/03/2018	1974 to 2018 March 16	187	92
MEDLINE (Ovid)	15/03/2018	1946 to Present with Daily Update	274	125
MEDLINE In-Process (Ovid)	16/03/2018	March 15 , 2018	84	68

Top-up search

Databases	Date searched	Version/files	No. retrieved	Post de-dupe
Cochrane Central Register of Controlled Trials (CENTRAL)	06/08/2018	Issue 7 of 12, July 2018	187	152
Cochrane Database of Systematic Reviews (CDSR)	06/08/2018	Issue 8 of 12, August 2018	2	1
Database of Abstracts of Reviews of Effect (DARE)	N/A	LEGACY DATABASE - NO UPDATE SINCE ORIGINAL SEARCH	0	0
Embase (Ovid)	06/08/2018	1974 to 2018 August 03	858	705
MEDLINE (Ovid)	06/08/2018	1946 to August 03, 2018	352	348
MEDLINE In-Process (Ovid)	06/08/2018	August 03, 2018	88	84
MEDLINE Epub Ahead of Print	06/08/2018	August 03, 2018	76	68
MHRA – Drug Safety Alerts	06/08/2018	N/A	0	n/a

C.2 Search history Medline

Database: Medline	
1	Colitis, Ulcerative/ (32987)
2	exp Proctitis/ (3053)
3	exp inflammatory bowel diseases/ (75028)
4	(inflamm* adj4 (colon* or bowel)).ti,ab. (39606)
5	(ulcer* adj4 colitis).tw. (32358)

Database: Medline
6 (pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis).tw. (4083)
7 ((total or sub-total or subtotal or extensive or left-sided or universal) adj colitis).tw. (598)
8 or/1-7 (94390)
9 exp glucocorticoids/ (190101)
10 prednisolone/ (32971)
11 budesonide/ (4217)
12 beclomethasone/ (3030)
13 cortisone/ (20315)
14 hydrocortisone/ (71981)
15 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (195985)
16 methotrexate/ (38313)
17 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (39039)
18 6-mercaptopurine/ (6315)
19 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (5586)
20 azathioprine/ (14798)
21 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (14464)
22 tacrolimus/ (15065)
23 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide).tw. (19144)
24 cyclosporine/ (29288)

Database: Medline
25 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin).tw. (48758)
26 mesalamine/ (3355)
27 sulfasalazine/ (4249)
28 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (5768)
29 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (4733)
30 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (289)
31 or/9-30 (435912)
32 8 and 31 (12442)
33 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (4930039)
34 32 and 33 (3059)
35 exp crohn disease/ (37290)
36 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (37837)
37 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (1587)
38 ((colitis or enteritis) adj4 granuloma*).tw. (648)
39 ileocoli*.tw. (1925)
40 (epithelioid adj4 granuloma*).tw. (1842)
41 exp inflammatory bowel diseases/ (75028)
42 (inflamm* adj4 bowel).tw. (35973)
43 or/35-42 (92978)
44 exp glucocorticoids/ (190101)
45 dexamethasone isonicotinate/ or dexamethasone/ (51008)
46 fluprednisolone/ (281)
47 methylprednisolone hemisuccinate/ or methylprednisolone/ (19252)
48 prednisolone/ (32971)
49 prednisone/ (39961)
50 hydrocortisone/ (71981)
51 cortisone/ (20315)
52 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or

Database: Medline

vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (197102)

53 methotrexate/ (38313)

54 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (39039)

55 6-mercaptopurine/ (6315)

56 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (5586)

57 azathioprine/ (14798)

58 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (14464)

59 mesalamine/ (3355)

60 sulfasalazine/ (4249)

61 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (5768)

62 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (4733)

63 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (289)

64 enteral nutrition/ (19487)

65 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (18406)

66 food, formulated/ (6245)

67 exp food/ (1215042)

68 exp diet/ (258677)

69 lactose/ (11264)

70 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (7013)

Database: Medline
71 (formula* adj4 (diet* or food*)).tw. (5857)
72 ((diet or nutrition) adj therapy).tw. (3175)
73 enteral nutrition.tw. (6821)
74 dh.fs. (48474)
75 exp anti-bacterial agents/ (677899)
76 exp nitroimidazoles/ (18134)
77 or/44-76 (2412648)
78 43 and 77 (19101)
79 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (4930039)
80 78 and 79 (4984)
81 Infliximab/ (9326)
82 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex).tw. (9412)
83 Adalimumab/ (4382)
84 (Adalimumab or d2e7 or humira).tw. (4481)
85 or/81-84 (14247)
86 43 and 85 (5079)
87 34 or 80 or 86 (9567)
88 Randomized Controlled Trial.pt. (497588)
89 Controlled Clinical Trial.pt. (99265)
90 Clinical Trial.pt. (547948)
91 exp Clinical Trials as Topic/ (332607)
92 Placebos/ (36441)
93 Random Allocation/ (99781)
94 Double-Blind Method/ (157733)
95 Single-Blind Method/ (26629)
96 Cross-Over Studies/ (45112)
97 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (990056)
98 (random$ adj3 allocat$).tw. (27830)
99 placebo$.tw. (192664)
100 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (154732)
101 (crossover$ or (cross adj over$)).tw. (71695)
102 or/88-101 (1755240)
103 Meta-Analysis.pt. (92040)
104 Network Meta-Analysis/ (226)
105 Meta-Analysis as Topic/ (17172)
106 Review.pt. (2334380)
107 exp Review Literature as Topic/ (10190)
108 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (107952)
109 (review$ or overview$).ti. (364972)
110 (systematic$ adj5 (review$ or overview$)).tw. (103479)
111 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (6797)
112 ((studies or trial$) adj2 (review$ or overview$)).tw. (34673)
113 (integrat$ adj3 (research or review$ or literature)).tw. (8116)
114 (pool$ adj2 (analy$ or data)).tw. (22232)
115 (handsearch$ or (hand adj3 search$)).tw. (7405)
116 (manual$ adj3 search$).tw. (4478)
117 or/103-116 (2543434)
118 102 or 117 (3977465)

Database: Medline
119 87 and 118 (3791)
120 animals/ not humans/ (4648315)
121 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (1888307)
122 119 not (120 or 121) (3603)
123 limit 122 to english language (3230)

C.3 Economic Literature search strategies

C.3.1 Overview

Sources searched:

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- Embase (Ovid)
- EconLit (Ovid)
- NHS Economic Evaluation Database (NHS EED) (legacy database)
- Health Technology Assessment (HTA Database)

Searches with the limit of the 2012 Crohn's disease guideline were carried out in March 2018 and updated in August 2018.

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	18/03/2018	1946 to August 16, 2018	661
MEDLINE in Process (Ovid)	18/03/2018	August 16, 2018	137
MEDLINE ePubs (Ovid)		August 16, 2018	30
Embase (Ovid)	18/03/2018	1974 to 2018 August 16	2024
EconLit (Ovid)	18/03/2018	1886 to August 09, 2018	2
NHS Economic Evaluation Database (NHS EED) (legacy database)	18/03/2018	Issue 2 of 4, April 2015	20
Health Technology Assessment (HTA Database)	18/03/2018	Issue 4 of 4, October 2016	30
Total before de-duplication			2904
No. duplicates removed			557
Total included for sifting			2347

C.3.2 Search strategy Ovid MEDLINE(R)

Database: Ovid MEDLINE(R)
1 exp crohn disease/ (36106)
2 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (36823)
3 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (1509)
4 ((colitis or enteritis) adj4 granuloma*).tw. (617)

Database: Ovid MEDLINE(R)
5 ileocoli*.tw. (1820)
6 (epithelioid adj4 granuloma*).tw. (1788)
7 exp inflammatory bowel diseases/ (73360)
8 (inflamm* adj4 bowel).tw. (35701)
9 or/1-8 (90739)
10 exp glucocorticoids/ (182115)
11 dexamethasone isonicotinate/ or dexamethasone/ (48901)
12 fluprednisolone/ (267)
13 methylprednisolone hemisuccinate/ or methylprednisolone/ (18414)
14 prednisolone/ (31506)
15 prednisone/ (37854)
16 hydrocortisone/ (69084)
17 cortisone/ (19517)
18 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (189390)
19 methotrexate/ (35823)
20 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (36496)
21 6-mercaptopurine/ (6070)
22 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (5349)
23 azathioprine/ (14141)
24 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (13738)
25 mesalamine/ (3229)
26 sulfasalazine/ (3947)

Database: Ovid MEDLINE(R)
27 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (5595)
28 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (4422)
29 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (279)
30 enteral nutrition/ (18317)
31 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (17487)
32 food, formulated/ (5720)
33 exp food/ (1182387)
34 exp diet/ (252800)
35 lactose/ (10902)
36 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (6679)
37 (formula* adj4 (diet* or food*)).tw. (5762)
38 ((diet or nutrition) adj therapy).tw. (3127)
39 enteral nutrition.tw. (6540)
40 dh.fs. (47040)
41 exp anti-bacterial agents/ (655842)
42 exp nitroimidazoles/ (17409)
43 or/10-42 (2336716)
44 9 and 43 (18604)
45 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018*).ed. (5141969)
46 44 and 45 (5223)
47 Infliximab/ (9109)
48 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab).tw. (9168)
49 Adalimumab/ (4383)
50 (Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa).tw. (4454)
51 (Vedolizumab or Entyvio).tw. (232)
52 Ustekinumab/ (667)
53 (Ustekinumab or "cnto 1275" or cnto-1275 or stelara).tw. (826)
54 Mycophenolic Acid/ (7356)
55 (Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw. (10579)
56 or/47-55 (26369)
57 9 and 56 (5492)
58 46 or 57 (9956)
59 Economics/ (26947)

Database: Ovid MEDLINE(R)
60 exp "Costs and Cost Analysis"/ (217637)
61 Economics, Dental/ (1897)
62 exp Economics, Hospital/ (23025)
63 exp Economics, Medical/ (14037)
64 Economics, Nursing/ (3981)
65 Economics, Pharmaceutical/ (2794)
66 Budgets/ (10947)
67 exp Models, Economic/ (13477)
68 Markov Chains/ (12918)
69 Monte Carlo Method/ (25609)
70 Decision Trees/ (10269)
71 econom$.tw. (206754)
72 cba.tw. (9402)
73 cea.tw. (18979)
74 cua.tw. (907)
75 markov$.tw. (15835)
76 (monte adj carlo).tw. (26883)
77 (decision adj3 (tree$ or analys$)).tw. (11253)
78 (cost or costs or costing$ or costly or costed).tw. (402915)
79 (price$ or pricing$).tw. (29575)
80 budget$.tw. (21413)
81 expenditure$.tw. (43985)
82 (value adj3 (money or monetary)).tw. (1816)
83 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3242)
84 or/59-83 (824187)
85 "Quality of Life"/ (165425)
86 quality of life.tw. (194851)
87 "Value of Life"/ (5608)
88 Quality-Adjusted Life Years/ (10350)
89 quality adjusted life.tw. (9007)
90 (qaly$ or qald$ or qale$ or qtime$).tw. (7387)
91 disability adjusted life.tw. (2110)
92 daly$.tw. (1964)
93 Health Status Indicators/ (22479)
94 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (20001)
95 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1204)
96 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4123)
97 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (26)
98 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (361)
99 (euroqol or euro qol or eq5d or eq 5d).tw. (6865)
100 (qol or hql or hqol or hrqol).tw. (36723)
101 (hye or hyes).tw. (57)
102 health$ year$ equivalent$.tw. (38)
103 utilit$.tw. (149166)
104 (hui or hui1 or hui2 or hui3).tw. (1118)

Database: Ovid MEDLINE(R)
105 disutili$.tw. (321)
106 rosser.tw. (81)
107 quality of wellbeing.tw. (10)
108 quality of well-being.tw. (361)
109 qwb.tw. (185)
110 willingness to pay.tw. (3557)
111 standard gamble$.tw. (738)
112 time trade off.tw. (927)
113 time tradeoff.tw. (223)
114 tto.tw. (793)
115 or/85-114 (427121)
116 84 or 115 (1192199)
117 58 and 116 (955)
118 animals/ not humans/ (4455462)
119 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (1838914)
120 117 not (118 or 119) (907)
121 limit 120 to english language (833)
122 limit 121 to ed=20180318-20180817 (63)

C.3.3 Search strategy Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
1 exp crohn disease/ (0)
2 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (3737)
3 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (55)
4 ((colitis or enteritis) adj4 granuloma*).tw. (36)
5 ileocoli*.tw. (180)
6 (epithelioid adj4 granuloma*).tw. (151)
7 exp inflammatory bowel diseases/ (0)
8 (inflamm* adj4 bowel).tw. (4851)
9 or/1-8 (7470)
10 exp glucocorticoids/ (0)
11 dexamethasone isonicotinate/ or dexamethasone/ (0)
12 fluprednisolone/ (0)
13 methylprednisolone hemisuccinate/ or methylprednisolone/ (0)
14 prednisolone/ (0)
15 prednisone/ (0)
16 hydrocortisone/ (0)
17 cortisone/ (0)
18 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (12621)

19 methotrexate/ (0)

20 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (2808)

21 6-mercaptopurine/ (0)

22 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (336)

23 azathioprine/ (0)

24 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (976)

25 mesalamine/ (0)

26 sulfasalazine/ (0)

27 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (539)

28 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (310)

29 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (11)

30 enteral nutrition/ (0)

31 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (1789)

32 food, formulated/ (0)

33 exp food/ (0)

34 exp diet/ (0)

35 lactose/ (0)

36 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (504)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
37 (formula* adj4 (diet* or food*)).tw. (673)
38 ((diet or nutrition) adj therapy).tw. (275)
39 enteral nutrition.tw. (748)
40 dh.fs. (0)
41 exp anti-bacterial agents/ (0)
42 exp nitroimidazoles/ (0)
43 or/10-42 (19527)
44 9 and 43 (722)
45 2012-03-01:2018-08-17-0600.(dt). (2070518)
46 44 and 45 (558)
47 Infliximab/ (0)
48 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab).tw. (1243)
49 Adalimumab/ (0)
50 (Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa).tw. (854)
51 (Vedolizumab or Entyvio).tw. (192)
52 Ustekinumab/ (0)
53 (Ustekinumab or "cnto 1275" or cnto-1275 or stelara).tw. (297)
54 Mycophenolic Acid/ (0)
55 (Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw. (967)
56 or/47-55 (2993)
57 9 and 56 (712)
58 46 or 57 (1161)
59 Economics/ (0)
60 exp "Costs and Cost Analysis"/ (0)
61 Economics, Dental/ (0)
62 exp Economics, Hospital/ (0)
63 exp Economics, Medical/ (0)
64 Economics, Nursing/ (0)
65 Economics, Pharmaceutical/ (0)
66 Budgets/ (0)
67 exp Models, Economic/ (0)
68 Markov Chains/ (0)
69 Monte Carlo Method/ (0)
70 Decision Trees/ (0)
71 econom$.tw. (33358)
72 cba.tw. (349)
73 cea.tw. (1464)
74 cua.tw. (136)
75 markov$.tw. (4290)
76 (monte adj carlo).tw. (13659)
77 (decision adj3 (tree$ or analys$)).tw. (1583)
78 (cost or costs or costing$ or costly or costed).tw. (72750)
79 (price$ or pricing$).tw. (4492)
80 budget$.tw. (3942)
81 expenditure$.tw. (5132)
82 (value adj3 (money or monetary)).tw. (271)
83 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (500)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
84 or/59-83 (126351)
85 "Quality of Life"/ (0)
86 quality of life.tw. (30058)
87 "Value of Life"/ (0)
88 Quality-Adjusted Life Years/ (0)
89 quality adjusted life.tw. (1252)
90 (qaly$ or qald$ or qale$ or qtime$).tw. (1070)
91 disability adjusted life.tw. (371)
92 daly$.tw. (332)
93 Health Status Indicators/ (0)
94 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2209)
95 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (597)
96 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (578)
97 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (4)
98 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (15)
99 (euroqol or euro qol or eq5d or eq 5d).tw. (1319)
100 (qol or hql or hqol or hrqol).tw. (5606)
101 (hye or hyes).tw. (4)
102 health$ year$ equivalent$.tw. (2)
103 utilit$.tw. (23559)
104 (hui or hui1 or hui2 or hui3).tw. (148)
105 disutili$.tw. (46)
106 rosser.tw. (12)
107 quality of wellbeing.tw. (5)
108 quality of well-being.tw. (18)
109 qwb.tw. (7)
110 willingness to pay.tw. (662)
111 standard gamble$.tw. (50)
112 time trade off.tw. (93)
113 time tradeoff.tw. (6)
114 tto.tw. (91)
115 or/85-114 (55456)
116 84 or 115 (174671)
117 58 and 116 (142)
118 animals/ not humans/ (0)
119 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (130533)
120 117 not (118 or 119) (142)
121 limit 120 to english language (140)
122 2018-03-18:2018-08-17-0600.(dt). (373561)
123 121 and 122 (20)

C.3.4 Search strategy Ovid MEDLINE(R) Epub ahead of print

Database: Ovid MEDLINE(R) Epub ahead of print

1 exp crohn disease/ (0)
2 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (649)
3 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (6)
4 ((colitis or enteritis) adj4 granuloma*).tw. (8)
5 ileocoli*.tw. (35)
6 (epithelioid adj4 granuloma*).tw. (16)
7 exp inflammatory bowel diseases/ (0)
8 (inflamm* adj4 bowel).tw. (954)
9 or/1-8 (1336)
10 exp glucocorticoids/ (0)
11 dexamethasone isonicotinate/ or dexamethasone/ (0)
12 fluprednisolone/ (0)
13 methylprednisolone hemisuccinate/ or methylprednisolone/ (0)
14 prednisolone/ (0)
15 prednisone/ (0)
16 hydrocortisone/ (0)
17 cortisone/ (0)
18 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (2272)
19 methotrexate/ (0)
20 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (548)
21 6-mercaptopurine/ (0)
22 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (65)
23 azathioprine/ (0)
24 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or

Database: Ovid MEDLINE(R) Epub ahead of print

imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (154)

25 mesalamine/ (0)

26 sulfasalazine/ (0)

27 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (79)

28 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (53)

29 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (2)

30 enteral nutrition/ (0)

31 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (372)

32 food, formulated/ (0)

33 exp food/ (0)

34 exp diet/ (0)

35 lactose/ (0)

36 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (77)

37 (formula* adj4 (diet* or food*)).tw. (109)

38 ((diet or nutrition) adj therapy).tw. (46)

39 enteral nutrition.tw. (142)

40 dh.fs. (0)

41 exp anti-bacterial agents/ (0)

42 exp nitroimidazoles/ (0)

43 or/10-42 (3559)

44 9 and 43 (121)

45 2012-03-01:2018-08-17-0600.(dt). (297160)

46 44 and 45 (109)

47 Infliximab/ (0)

48 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab).tw. (212)

49 Adalimumab/ (0)

50 (Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa).tw. (208)

51 (Vedolizumab or Entyvio).tw. (60)

52 Ustekinumab/ (0)

53 (Ustekinumab or "cnto 1275" or cnto-1275 or stelara).tw. (88)

54 Mycophenolic Acid/ (0)

55 (Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw. (165)

56 or/47-55 (594)

Database: Ovid MEDLINE(R) Epub ahead of print
57 9 and 56 (147)
58 46 or 57 (236)
59 Economics/ (0)
60 exp "Costs and Cost Analysis"/ (0)
61 Economics, Dental/ (0)
62 exp Economics, Hospital/ (0)
63 exp Economics, Medical/ (0)
64 Economics, Nursing/ (0)
65 Economics, Pharmaceutical/ (0)
66 Budgets/ (0)
67 exp Models, Economic/ (0)
68 Markov Chains/ (0)
69 Monte Carlo Method/ (0)
70 Decision Trees/ (0)
71 econom$.tw. (6227)
72 cba.tw. (55)
73 cea.tw. (335)
74 cua.tw. (20)
75 markov$.tw. (864)
76 (monte adj carlo).tw. (2321)
77 (decision adj3 (tree$ or analys$)).tw. (359)
78 (cost or costs or costing$ or costly or costed).tw. (12415)
79 (price$ or pricing$).tw. (864)
80 budget$.tw. (621)
81 expenditure$.tw. (1208)
82 (value adj3 (money or monetary)).tw. (59)
83 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (41)
84 or/59-83 (22030)
85 "Quality of Life"/ (0)
86 quality of life.tw. (6274)
87 "Value of Life"/ (0)
88 Quality-Adjusted Life Years/ (0)
89 quality adjusted life.tw. (300)
90 (qaly$ or qald$ or qale$ or qtime$).tw. (265)
91 disability adjusted life.tw. (84)
92 daly$.tw. (74)
93 Health Status Indicators/ (0)
94 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (498)
95 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (78)
96 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (123)
97 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
98 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (7)
99 (euroqol or euro qol or eq5d or eq 5d).tw. (310)
100 (qol or hql or hqol or hrqol).tw. (1248)
101 (hye or hyes).tw. (0)

Database: Ovid MEDLINE(R) Epub ahead of print
102 health$ year$ equivalent$.tw. (0)
103 utilit$.tw. (5039)
104 (hui or hui1 or hui2 or hui3).tw. (25)
105 disutili$.tw. (14)
106 rosser.tw. (2)
107 quality of wellbeing.tw. (1)
108 quality of well-being.tw. (8)
109 qwb.tw. (2)
110 willingness to pay.tw. (147)
111 standard gamble$.tw. (13)
112 time trade off.tw. (22)
113 time tradeoff.tw. (0)
114 tto.tw. (24)
115 or/85-114 (11696)
116 84 or 115 (32129)
117 58 and 116 (30)
118 animals/ not humans/ (0)
119 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (9333)
120 117 not (118 or 119) (30)
121 limit 120 to english language (30)

C.3.5 Search stretgy Embase

Database: Embase
1 exp crohn disease/ (76932)
2 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (65413)
3 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (856)
4 ((colitis or enteritis) adj4 granuloma*).tw. (712)
5 ileocoli*.tw. (2722)
6 (epithelioid adj4 granuloma*).tw. (2392)
7 exp inflammatory bowel diseases/ (120414)
8 (inflamm* adj4 bowel).tw. (64404)
9 or/1-8 (150217)
10 exp glucocorticoid/ (616578)
11 dexamethasone isonicotinate/ or dexamethasone/ (128739)
12 fluprednisolone/ (105)
13 methylprednisolone sodium succinate/ or methylprednisolone/ (84882)
14 prednisolone/ (107696)
15 prednisone/ (149134)
16 hydrocortisone/ (109848)
17 cortisone/ (11627)
18 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or

Database: Embase

solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (256440)

19 methotrexate/ (154085)

20 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (62620)

21 mercaptopurine/ (22885)

22 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (8568)

23 azathioprine/ (82532)

24 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (26657)

25 mesalazine/ (15704)

26 salazosulfapyridine/ (22485)

27 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (10047)

28 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (8042)

29 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (816)

30 enteric feeding/ (26728)

31 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (28517)

32 elemental diet/ (3096)

33 exp food/ (841164)

34 exp diet/ (269657)

Database: Embase
35 lactose/ (17697)
36 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (9669)
37 (formula* adj4 (diet* or food*)).tw. (7408)
38 ((diet or nutrition) adj therapy).tw. (4041)
39 enteral nutrition.tw. (12017)
40 exp antiinfective agent/ (2660884)
41 exp nitroimidazole derivative/ (148367)
42 or/10-41 (4138804)
43 9 and 42 (55935)
44 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018*).dc. (8462437)
45 43 and 44 (24120)
46 Infliximab/ (41318)
47 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab).tw. (23810)
48 Adalimumab/ (25235)
49 (Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa).tw. (15473)
50 vedolizumab/ (1745)
51 (Vedolizumab or Entyvio).tw. (1324)
52 Ustekinumab/ (4001)
53 (Ustekinumab or "cnto 1275" or cnto-1275 or stelara).tw. (2662)
54 Mycophenolic Acid/ (14059)
55 (Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw. (22747)
56 or/46-55 (80422)
57 9 and 56 (20176)
58 45 or 57 (38231)
59 exp Health Economics/ (729188)
60 exp "Health Care Cost"/ (249899)
61 exp Pharmacoeconomics/ (180662)
62 Monte Carlo Method/ (31885)
63 Decision Tree/ (9339)
64 econom$.tw. (293506)
65 cba.tw. (11683)
66 cea.tw. (29536)
67 cua.tw. (1219)
68 markov$.tw. (23673)
69 (monte adj carlo).tw. (38746)
70 (decision adj3 (tree$ or analys$)).tw. (17531)
71 (cost or costs or costing$ or costly or costed).tw. (611573)
72 (price$ or pricing$).tw. (46206)
73 budget$.tw. (32011)
74 expenditure$.tw. (62008)
75 (value adj3 (money or monetary)).tw. (2812)
76 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (7648)
77 or/59-76 (1447554)
78 "Quality of Life"/ (371934)
79 Quality Adjusted Life Year/ (19895)

Database: Embase
80 Quality of Life Index/ (2328)
81 Short Form 36/ (20897)
82 Health Status/ (109774)
83 quality of life.tw. (338752)
84 quality adjusted life.tw. (14653)
85 (qaly$ or qald$ or qale$ or qtime$).tw. (15121)
86 disability adjusted life.tw. (2819)
87 daly$.tw. (2869)
88 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (34298)
89 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1927)
90 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (7251)
91 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (51)
92 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (401)
93 (euroqol or euro qol or eq5d or eq 5d).tw. (14466)
94 (qol or hql or hqol or hrqol).tw. (73856)
95 (hye or hyes).tw. (110)
96 health$ year$ equivalent$.tw. (40)
97 utilit$.tw. (228866)
98 (hui or hui1 or hui2 or hui3).tw. (1794)
99 disutili$.tw. (683)
100 rosser.tw. (102)
101 quality of wellbeing.tw. (30)
102 quality of well-being.tw. (434)
103 qwb.tw. (227)
104 willingness to pay.tw. (6205)
105 standard gamble$.tw. (991)
106 time trade off.tw. (1419)
107 time tradeoff.tw. (260)
108 tto.tw. (1331)
109 or/78-108 (783297)
110 77 or 109 (2106335)
111 58 and 110 (5009)
112 nonhuman/ not human/ (4012321)
113 Abstract report/ or Conference abstract/ or Conference paper/ or Conference review/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (5499853)
114 111 not (112 or 113) (2803)
115 limit 114 to english language (2656)
116 (20180317* or 20180318* or 20180319* or 2018032* or 2018033* or 201804* or 201805* or 201806* or 201807* or 201808*).dc. (764006)
117 115 and 116 (166)

C.3.6 Search strategy EconLit

Database: EconLit
1 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (6)
2 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (0)
3 ((colitis or enteritis) adj4 granuloma*).tw. (0)
4 ileocoli*.tw. (0)
5 (epithelioid adj4 granuloma*).tw. (0)
6 (inflamm* adj4 bowel).tw. (11)
7 or/1-6 (15)
8 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (95)
9 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (6)
10 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (1)
11 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (1)
12 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (1)
13 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo

Database: EconLit
sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (0)
14 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (0)
15 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (12)
16 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (1)
17 (formula* adj4 (diet* or food*)).tw. (24)
18 ((diet or nutrition) adj therapy).tw. (1)
19 enteral nutrition.tw. (1)
20 or/8-19 (142)
21 7 and 20 (1)
22 limit 21 to yr=2012-2018 (1)
23 21 and 22 (1)
24 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab).tw. (13)
25 (Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa).tw. (5)
26 (Vedolizumab or Entyvio).tw. (1)
27 (Ustekinumab or "cnto 1275" or cnto-1275 or stelara).tw. (0)
28 (Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw. (2)
29 or/24-28 (16)
30 7 and 29 (2)
31 23 or 30 (2)
32 limit 31 to yr="2018 -Current" (1)

C.3.7 Search strategy NHS EED and HTA

Database: NHS EED and HTA
#1 [mh "crohn disease"] 1173
#2 (crohn or crohn's or crohns) near/4 (disease* or colitis):ti,ab,kw 2943
#3 (ileitis or enteritis) near/4 (terminal or regional):ti,ab,kw 8
#4 (colitis or enteritis) near/4 granuloma*:ti,ab,kw 0
#5 ileocoli*:ti,ab,kw 81
#6 (epithelioid near/4 granuloma*):ti,ab,kw 10
#7 [mh "inflammatory bowel diseases"] 2416
#8 (inflamm* near/4 bowel):ti,ab,kw 1885
#9 {or #1-#8} 4789
#10 [mh glucocorticoids] 4244
#11 [mh ^"dexamethasone isonicotinate"] or [mh ^dexamethasone] 2921
#12 [mh ^fluprednisolone] 16
#13 [mh ^"methylprednisolone hemisuccinate"] or [mh ^methylprednisolone] 1818
#14 [mh ^prednisolone] 2119
#15 [mh ^prednisone] 3146
#16 [mh ^hydrocortisone] 5241
#17 [mh ^cortisone] 89
#18 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or

Database: NHS EED and HTA

budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson):ti,ab,kw 39652

#19 [mh ^methotrexate] 3276

#20 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate):ti,ab,kw 8473

#21 [mh ^6-mercaptopurine] 269

#22 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine):ti,ab,kw 226

#23 [mh ^azathioprine] 1142

#24 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim):ti,ab,kw 2810

#25 [mh ^mesalamine] 445

#26 [mh ^sulfasalazine] 430

#27 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476):ti,ab,kw 1341

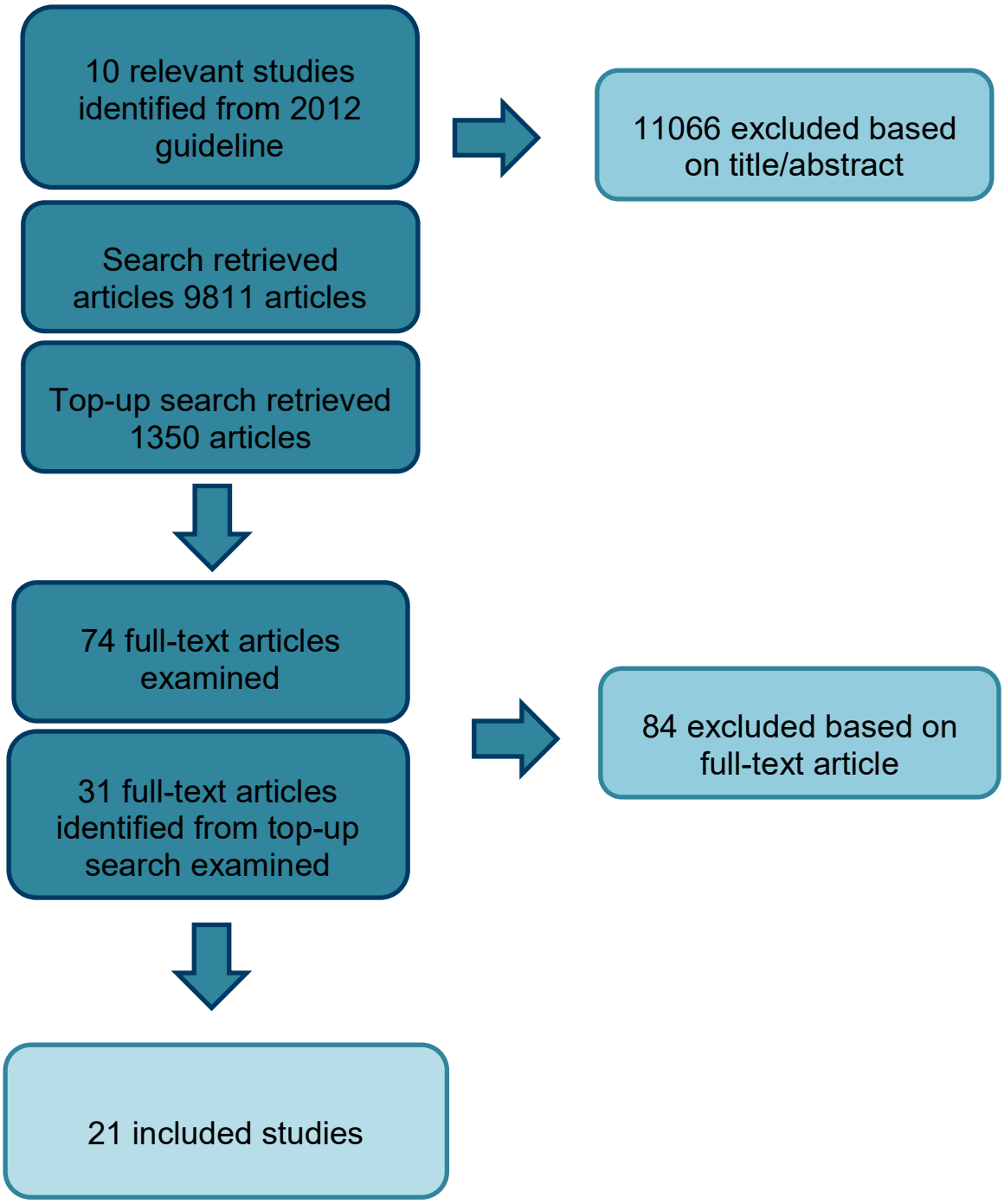
#28 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin):ti,ab,kw 1150

#29 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal):ti,ab,kw 131

#30 [mh ^"enteral nutrition"] 1862

Database: NHS EED and HTA	
#31	((enteral* or force* or tube*) near/4 (nutrition* or feeding*)):ti,ab,kw 4549
#32	[mh ^"food, formulated"] 744
#33	[mh food] 28633
#34	[mh diet] 16450
#35	[mh ^lactose] 277
#36	((polymeric or elemental or liquid or peptide or whole protein) near (diet* or food* or formula*)):ti,ab,kw 2411
#37	(formula* near/4 (diet* or food*)):ti,ab,kw 1488
#38	((diet or nutrition) near therapy):ti,ab,kw 6397
#39	enteral nutrition:ti,ab,kw 4129
#40	Any MeSH descriptor with qualifier(s): [Diet therapy - DH] 7247
#41	((enteral* or force* or tube*) near/4 (nutrition* or feeding*)):ti,ab,kw 4549
#42	[mh "anti-bacterial agents"] 11141
#43	[mh nitroimidazoles] 2319
#44	{or #10-#43} 109705
#45	#9 and #44 Publication Year from 2012 to 2018 656
#46	[mh ^Infliximab] 492
#47	(infliximab or "mab ca2" or remicade or avakine or flixabi or revellex or inflectra or ixifi or renflexis or remsima or flixabi or infimab):ti,ab,kw 1588
#48	[mh ^Adalimumab] 335
#49	(Adalimumab or d2e7 or humira or Amjevita or Cyltezo or Exemptia or Adfrar or amgevita or imraldi or solymbic or trudexa):ti,ab,kw 1615
#50	(Vedolizumab or Entyvio):ti,ab,kw 130
#51	[mh ^Ustekinumab] 62
#52	(Ustekinumab or "cnto 1275" or cnto-1275 or stelara):ti,ab,kw 319
#53	[mh ^"Mycophenolic Acid"] 906
#54	(Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185):ti,ab,kw 2975
#55	{or #46-#54} 6056
#56	#9 and #55 798
#57	#45 or #56 1257

Appendix D: Clinical evidence study selection



Appendix E: References

E.1 Clinical studies

Included studies

Ardizzone S, Maconi G, Sampietro GM, et al. (2004) Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease.. Gastroenterology 127(3), 730-40

Armuzzi A, Felice C, Papa A, Marzo M, et al. (2013) Prevention of postoperative recurrence with azathioprine or infliximab in patients with Crohn's disease: an open-label pilot study. Journal of Crohn's & colitis 7(12), e623-9

Brignola C, Cottone M, Pera A, Ardizzone S, et al. (1995) Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group.. Gastroenterology 108(2), 345-9

Caprilli R, Andreoli A, Capurso L, Corrao G, et al. (1994) Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC).. Alimentary pharmacology & therapeutics 8(1), 35-43

D'Haens GR, Vermeire S, Van Assche G, et al. (2008) Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial.. Gastroenterology 135(4), 1123-9

Ewe K, Herfarth C, Malchow H, et al. (1989) Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: a multicenter trial.. Digestion 42(4), 224-32

Ewe K, Bottger T, Buhr HJ, et al. (1999) Low-dose budesonide treatment for prevention of postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group.. European journal of gastroenterology & hepatology 11(3), 277-82

Hanauer SB, Korelitz BI, Rutgeerts P, et al. (2004) Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial.. Gastroenterology 127(3), 723-9

Hellers G, Cortot A, Jewell D, et al. (1999) Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The IOIBD Budesonide Study Group.. Gastroenterology 116(2), 294-300

Lochs H, Mayer M, Fleig WE, et al. (2000) Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI.. Gastroenterology 118(2), 264-73

Lopez-Sanroman A, Vera-Mendoza I, Domenech E, et al. (2017) Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial. Journal of Crohn's & colitis 11(11), 1293-1301

Mañosa M, Cabré E, Bernal I, et al. (2013) Addition of metronidazole to azathioprine for the prevention of postoperative recurrence of Crohn's disease: a randomized, double-blind, placebo-controlled trial. Inflammatory bowel diseases 19(9), 1889-1895

McLeod RS, Wolff BG, Steinhart AH, et al (1995) Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. Gastroenterology 109(2), 404-13

Mowat C, Arnott I, Cahill A, et al. (2016) Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. The lancet gastroenterology and hepatology 1(4), 273-282

Regueiro M, Schraut W, Baidoo L, et al. (2009) Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 136(2), 441-50.e1; quiz 716

Regueiro M, Feagan BG, Zou B, et al. (2016) Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. Gastroenterology 150(7), 1568-1578

Rutgeerts P, Hiele M, Geboes K, et al. (1995) Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection.. Gastroenterology 108(6), 1617-21

Savarino E, Bodini G, Dulbecco P, et al. (2013) Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial.. The American journal of gastroenterology 108(11), 1731-42

Tursi A, Elisei W, Picchio M, et al. (2014) Comparison of the effectiveness of infliximab and adalimumab in preventing postoperative recurrence in patients with Crohn's disease: an open-label, pilot study. Techniques in Coloproctology 18(11), 1041-6

Wenckert A, Kristensen M, Eklund AE, et al. (1978) The long-term prophylactic effect of salazosulphapyridine (Salazopyrin) in primarily resected patients with Crohn's disease. A controlled double-blind trial.. Scandinavian journal of gastroenterology 13(2), 161-7

Yoshida K, Fukunaga K, Ikeuchi H, et al. (2012) Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial. Inflammatory Bowel Diseases 18(9), 1617-23

Excluded studies

Allocca M, Landi R, Bonovas S, Fiorino G, et al. (2017) Effectiveness of Mesalazine, Thiopurines and Tumour Necrosis Factor Antagonists in Preventing Post-Operative Crohn's Disease Recurrence in a Real-Life Setting. Digestion , 166-172

Angelberger S, Schaeffeler E, Teml A, et al. (2013) Mucosal improvement in patients with moderate to severe postoperative endoscopic recurrence of Crohn's disease and azathioprine metabolite levels. Inflammatory Bowel Diseases 19(3), 590-8

Bakouny Z, Yared F, El Rassy E, et al. (2018) Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease: A Systematic Review and Network Meta-Analysis of Prospective Trials.. Journal of clinical gastroenterology ,

Beaupel N, Brouquet A, Abdalla S, et al. (2017) Preoperative oral polymeric diet enriched with transforming growth factor-beta 2 (Modulen) could decrease postoperative morbidity after surgery for complicated ileocolonic Crohn's disease. Scandinavian Journal of Gastroenterology 52(1), 5-10

Behm B W, and Bickston S J (2008) Tumor necrosis factor-alpha antibody for maintenace of remission in Crohn's disease. Cochrane Database of Systematic Reviews (1), CD006893

Carla-Moreau A, Paul S, Roblin X, et al. (2015) Prevention and treatment of postoperative Crohn's disease recurrence with anti-TNF therapy: a meta-analysis of controlled trials. Digestive & Liver Disease 47(3), 191-6

Carla-Moreau A, Paul S, Roblin X, Genin C, et al. (2015) Prevention and treatment of postoperative Crohn's disease recurrence with anti-TNF therapy: a meta-analysis of controlled trials.. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 47(3), 191-6

Cruz P, Kamm Ma, Hamilton Al, et al. (2015) Crohn's disease management after intestinal resection: a randomised trial. Lancet (london, and england) 385(9976), 1406-1417

de Souza , G S, Vidigal F M, Chebli L A, et al. (2013) Effect of azathioprine or mesalazine therapy on incidence of re-hospitalization in sub-occlusive ileocecal Crohn's disease patients. Medical Science Monitor 19, 716-22

Doherty G, Bennett G, Patil S, et al. (2009) Interventions for prevention of post-operative recurrence of Crohn's disease.. The Cochrane database of systematic reviews (4), CD006873

Doherty GA, Bennett GC, Cheifetz AS, et al. (2010) Meta-analysis: targeting the intestinal microbiota in prophylaxis for post-operative Crohn's disease.. Alimentary pharmacology & therapeutics 31(8), 802-9

El-Hussuna A, Theede K, and Olaison G (2014) Increased risk of post-operative complications in patients with Crohn's disease treated with antitumour necrosis factor alpha agents - a systematic review. Danish Medical Journal 61(12), A4975

Feagan B, Gasink C, Lang Y, et al. (2015) A multicenter, double-blind, placebo-controlled pH3 study of ustekinumab, a human monoclonal antibody to IL-12/23p40, in patients with moderately-severely active Crohn's disease who are not naive or not refractory to anti-TNFa: uNITI-2. United European gastroenterology journal 3(6), 563-564

Feng JS, Li JY, Chen XY, et al. (2017) Strategies for Preventing Endoscopic Recurrence of Crohn's Disease 1 Year after Surgery: A Network Meta-Analysis. Gastroenterology Research and Practice 2017, 7896160

Ferrante M, Papamichael K, Duricova D, et al. (2014) Systematic versus endoscopy-driven treatment with azathioprine to prevent postoperative ileal Crohn's disease recurrence. Journal of crohn's and colitis. 8, S205-s206

Ferrante M, Papamichael K, Duricova D, et al. (2015) Systematic versus Endoscopy-driven Treatment with Azathioprine to Prevent Postoperative Ileal Crohn's Disease Recurrence. Journal of crohn's & colitis 9(8), 617-624

Gordon M, Taylor K, Akobeng AK, et al. (2014) Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews (8), CD010233

Hadigan Cbr, Braegger Cp, Vasilauskis E, et al. (1999) Pharmacokinetics of infliximab (Anti-TNFx) in children with Crohn's disease: a multicenter trial. Journal of pediatric gastroenterology and nutrition 29(4), 525

Hanai H, Iida T, Takeuchi K, Arai H, et al. (2012) Nutritional therapy versus 6-mercaptopurine as maintenance therapy in patients with Crohn's disease. Digestive & Liver Disease 44(8), 649-54

Kawalec P, Mikrut A, Wisniewska N, et al. (2013) Tumor necrosis factor-alpha antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease: systematic review and meta-analysis. Archives of Medical Science 9(5), 765-79

Kopylov U, Ben-Horin S, Zmora O, et al. (2012) Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. Inflammatory Bowel Diseases 18(12), 2404-13

Kuenzig M E, Rezaie A, Seow C H, et al. (2014) Budesonide for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews (8), CD002913

Loo Es, Dijkstra G, Ploeg Rj, et al. (2012) Prevention of postoperative recurrence of Crohn's disease (Structured abstract). Journal of Crohn's and Colitis 6(6), 637-646

Matsumoto T, Motoya S, Watanabe K, et al. (2016) Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: a Prospective, Randomized Trial. Journal of crohn's & colitis 10(11), 1259-1266

Nguyen D L, Solaimani P, Nguyen E T, et al. (2014) Antitumor necrosis factor alpha is more effective than conventional medical therapy for the prevention of postoperative recurrence of Crohn's disease: a meta-analysis. European Journal of Gastroenterology & Hepatology 26(10), 1152-9

Papamichael K, Archavlis E, Lariou C, et al. (2012) Adalimumab for the prevention and/or treatment of post-operative recurrence of Crohn's disease: a prospective, two-year, single center, pilot study. Journal of crohn's & colitis 6(9), 924-931

Papi C, Fasci Spurio, F, Margagnoni G, et al. (2012) Randomized controlled trials in prevention of postsurgical recurrence in Crohn's disease. Reviews on Recent Clinical Trials 7(4), 307-13

Patel V, Wang Y, MacDonald JK, et al. (2014) Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews (8), CD006884

Qiu Y, Mao R, Chen BL, et al. (2015) Systematic Review with Meta-analysis of Prospective Studies: Anti-tumour Necrosis Factor for Prevention of Postoperative Crohn's Disease Recurrence.. Journal of Crohn's & colitis 9(10), 918-27

Regueiro M, El-Hachem S, Kip Ke, et al. (2011) Postoperative infliximab is not associated with an increase in adverse events in Crohn's disease. Digestive diseases and sciences 56(12), 3610-3615

Regueiro M, Kip K, Baidoo L, et al. (2014) Postoperative therapy with infliximab prevents long-term Crohn's disease recurrence. Clinical gastroenterology and hepatology 12(9), 1494-502.e1

Regueiro M, Feagan Bg, Zou B, et al. (2015) Infliximab for prevention of recurrence of post-surgical crohn's disease following ileocolonic resection: a randomized, placebo-controlled study. Gastroenterology. 148(4 suppl. 1), S141

Rutgeerts P, Diamond Rh, Bala M, et al. (2006) Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointestinal endoscopy 63(3), 433-42; quiz 464

Singh S, Garg SK, Pardi DS, et al. (2015) Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis.. Gastroenterology 148(1), 64-76.e2; quiz e14

Sutherland LR, Martin F, Bailey RJ, et al. (1997) A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group.. Gastroenterology 112(4), 1069-77

Van Assche , G , Vermeire S, Ballet V, et al. (2012) Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut 61(2), 229-34

van Loo ES, Dijkstra G, Ploeg RJ, et al. (2012) Prevention of postoperative recurrence of Crohn's disease.. Journal of Crohn's & colitis 6(6), 637-46

Waterland P, Athanasiou T, and Patel H (2016) Post-operative abdominal complications in Crohn's disease in the biological era: Systematic review and meta-analysis.. World journal of gastrointestinal surgery 8(3), 274-83

Yamamoto T, Shiraki M, Nakahigashi M, et al. (2013) Enteral nutrition to suppress postoperative Crohn's disease recurrence: a five-year prospective cohort study. International Journal of Colorectal Disease 28(3), 335-40

Yamamoto T, Nakahigashi M, Saniabadi AR, et al. (2007) Impacts of long-term enteral nutrition on clinical and endoscopic disease activities and mucosal cytokines during remission in patients with Crohn's disease: A prospective study. Inflammatory Bowel Diseases 13(12), 1493-1501

Yang Z, Ye X, Wu Q, et al. (2014) A network meta-analysis on the efficacy of 5-aminosalicylates, immunomodulators and biologics for the prevention of postoperative recurrence in Crohn's disease.. International journal of surgery (London, and England) 12(5), 516-22

Yassin NA, Askari A, Warusavitarne J, et al. (2014) Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease.. Alimentary pharmacology & therapeutics 40(7), 741-9

Zhao Y, Ma T, Chen YF, He XY, et al. (2015) Biologics for the prevention of postoperative Crohn's disease recurrence: A systematic review and meta-analysis. Clinics & Research in Hepatology & Gastroenterology 39(5), 637-49

Top-up search: excluded

Allez M, Braegger F, Kempf C, et al. (2018) Efficacy of vedolizumab (VDZ) by disease localisation in Crohn's disease. Journal of crohn's and colitis. Conference: 13th congress of European crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S479

Bakouny Z, Yared F, El Rassy, et al. (2018) Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease: A Systematic Review and Network Meta-Analysis of Prospective Trials. Journal of Clinical Gastroenterology 06, 06

Berends S, Lowenberg M, Baert F, et al. (2018) Higher serum concentrations of vedolizumab are associated with superior endoscopic outcomes in Crohn's disease: data from the LOVE-CD trial. Journal of crohn's and colitis. Conference: 13th congress of European crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S63

Chalhoub J M, Rimmani H H, Gumaste V V, et al. (2017) Systematic Review and Meta-analysis: Adalimumab Monotherapy Versus Combination Therapy with Immunomodulators for Induction and Maintenance of Remission and Response in Patients with Crohn's Disease. Inflammatory Bowel Diseases 23(8), 1316-1327

Colman R J, Lawton R C, Dubinsky M C, et al. (2018) Methotrexate for the Treatment of Pediatric Crohn's Disease: A Systematic Review and Meta-analysis. Inflammatory Bowel Diseases 23, 23

Dziechciarz P, Horvath A, and Kierkus J (2016) Efficacy and safety of Adalimumab for paediatric Crohn's disease: A systematic review. Journal of Crohn's and Colitis 10(10), 1237-1244

El-Matary W, Otley A, Critch J, et al. 2017) Enteral Feeding Therapy for Maintaining Remission in Crohn's Disease: A Systematic Review. Jpen: Journal of Parenteral & Enteral Nutrition 41(4), 550-561

Engel T, Ungar B, Yung D E, et al. (2018) Vedolizumab in IBD-Lessons from real-world experience; A systematic review and pooled analysis. Journal of Crohn's and Colitis 12(2), 245-257

Estevinho M M, Afonso J, Rosa I, et al. (2017) A systematic review and meta-analysis of 6-thioguanine nucleotide levels and clinical remission in inflammatory bowel disease. Journal of Crohn's and Colitis 11(11), 1381-1392

Feagan B, Sandborn W J, Rutgeerts Paul, et al. (2018) Performance of Crohn's disease Clinical Trial Endpoints based upon Different Cutoffs for Patient Reported Outcomes or Endoscopic Activity: Analysis of EXTEND Data. Inflammatory Bowel Diseases 24(5), 932-942

Fukushima K, Sugita A, Futami K, et al. (2018) Postoperative therapy with infliximab for Crohn's disease: a 2-year prospective randomized multicenter study in Japan. Surgery Today 48(6), 584-590

Ganji-Arjenaki M, and Rafieian-Kopaei M (2018) Probiotics are a good choice in remission of inflammatory bowel diseases: A meta analysis and systematic review. Journal of Cellular Physiology 233(3), 2091-2103

Ghosh S, Gasink C, Gao L-L, et al. (2018) Number needed to treat to achieve clinical response at week 8 along with response or remission at week 52 with ustekinumab treatment vs. placebo from the phase 3 UNITI Crohn's disease studies, by population. Journal of crohn's and colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S450-s451

Ghosh S, Sattin B, Tornatore V, Gasink C, et al. (2018) Outcomes of maintenance ustekinumab therapy for Crohn's disease based on inflammatory burden: a post-hoc analysis of the UNITI trials. Journal of crohn's and colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S192-s193

Gordon M, Taylor K, Akobeng A K, et al. (2014) Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews 2017(12), CD010233

Hardi R, Bokemeyer B, Sandborn W, et al. (2018) Sustained clinical remission with vedolizumab in Moderate-to-Severe Crohn's disease: a GEMINI 2 post hoc analysis of Week 14 remitters. Journal of crohn's and colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S485

Kuenzig M E, Rezaie A, Seow C H, et al. (2014) Budesonide for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2014(8), CD002913

Lev-Tzion R, Griffiths A M, Leder O, et al. (2014) Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2014(2), CD006320

Lopez-Sanroman A, Vera-Mendoza I, Domenech E, et al. (2017) Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial. Journal of Crohn's & colitis 11(11), 1293-1301

Ma C, Dutton S J, Cipriano L E, et al. 2018) Systematic review with meta-analysis: prevalence, risk factors and costs of aminosalicylate use in Crohn's disease. Alimentary Pharmacology & Therapeutics 48(2), 114-126

Mowat C, Arnott I, Cahill A, et al. (2016) Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. The Lancet. Gastroenterology & Hepatology 1(4), 273-282

Panaccione R, Colombel J-F, Bossuyt P, et al. (2018) Long-term cost-effectiveness of tight control for Crohn's disease with adalimumab-based treatment: economic evaluation beyond 48 weeks of CALM trial. Journal of crohn's and colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S74-s75

Patel V, Wang Y, Macdonald J K, et al. (2014) Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2014(8), CD006884

Roblin X, Boschetti G, Williet N, et al. (2017) Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. Alimentary Pharmacology & Therapeutics 46(2), 142-149

Sandborn Wj, Rutgeerts P, Gasink C, et al. (2018) Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. Alimentary pharmacology & therapeutics (no pagination),

Satsangi J, Kennedy N A, Mowat C, et al. (2017) A randomised, double-blind, parallel-group trial to assess mercaptopurine versus placebo to prevent or delay recurrence of Crohn’s disease following surgical resection (TOPPIC). NIHR Journals Library Efficacy and Mechanism Evaluation 04(4), 09

Schlussel A T, Cherng N B, and Alavi K (2017) Current trends and challenges in the postoperative medical management of Crohn's disease: A systematic review. American Journal of Surgery 214(5), 931-937

Shen F C, Zhang H J, Zhao X D, et al. (2012) Purine analogues compared with mesalamine or 5-ASA for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. International Journal of Clinical Practice 66(8), 758-766

Vermeire S, Loftus E, Khalid J, et al. (2018) Vedolizumab treatment persistence up to 3 years: post hoc analysis in vedolizumab-naive patients from the GEMINI LTS study. Journal of crohn's and colitis. Conference: 13th congress of European crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S30-s31

Walters T D, Faubion W A, Griffiths A M, et al. (2017) Growth Improvement with Adalimumab Treatment in Children with Moderately to Severely Active Crohn's Disease. Inflammatory Bowel Diseases 23(6), 967-975

Zarubova K, Hradsky O, Copova I, et al. (2017) Endoscopic Recurrence 6 Months After Ileocecal Resection in Children With Crohn Disease Treated With Azathioprine. Journal of Pediatric Gastroenterology & Nutrition 65(2), 207-211

E.2 Health economics

Included studies

Ananthakrishnan A N, Hur C, Juillerat P et al. (2011) Strategies for the prevention of postoperative recurrence in Crohn's disease: results of a decision analysis. American Journal of Gastroenterology 106(11), 2009-17

Doherty GA, Miksad RA, Cheifetz AS et al. (2012) Comparative cost-effectiveness of strategies to prevent postoperative clinical recurrence of Crohn's disease. Inflammatory Bowel Diseases 18(9), 1608-1616

Excluded studies

Bodger K, Kikuchi T, Hughes D (2009). Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Alimentary Pharmacology & Therapeutics 30(3), 265-74

Candia R, Naimark D, Sander B, Nguyen GC (2017). Cost-utility Analysis: Thiopurines Plus Endoscopy-guided Biological Step-up Therapy is the Optimal Management of Postoperative Crohn's Disease. Inflammatory Bowel Diseases 23(11),1930-1940

Wright EK, Kamm MA, De Cruz P, et al. (2015) Effect of intestinal resection on quality of life in Crohn's disease. Journal of Crohn's and Colitis 9(6),452-62

Other references

Burisch J, Jess T, Martinato et al. (2013) The burden of inflammatory bowel disease in Europe. Journal of Crohn's and Colitis 7: 322-337

Candy S, Wright J, Gerber M et al. (1995) A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 37: 674-8

Chu TPC, Moran GW and Card TR (2017) The pattern of underlying cause of death in patients with inflammatory bowel disease in England: a record linkage study. Journal of Crohn's and Colitis, 578-585

Doherty GA, Miksad RA, Cheifetz AS et al. (2012) Comparative cost-effectiveness of strategies to prevent postoperative clinical recurrence of Crohn's disease. Inflammatory Bowel Diseases 18(9), 1608-1616

Doherty G, Bennett G, Patil S *et al. (2009)* Interventions for prevention of postoperative recurrence of Crohn's disease. Cochrane Database Syst Rev (4) CD006873

Drug Topics Red Book (2010). PDR Network, LLC

Gregor JC, McDonald JWD, Klar N, et al. (1997) An evaluation of utility measurements in Crohn's disease. Inflamm Bowel Dis. 3:265–276

Kaltenthaler E, Tappenden P, Paisley S et al. (2011). NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from http://www.nicedsu.org.uk

Kaplan GG, Hur C, Korzenik J et al. (2007) Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: a cost-effectiveness analysis. Aliment Pharmacol 26: 1509-20

Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. (2008) Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology 135: 1907–1913

Lichtenstein GR, Feagan BG, Cohen RD e t al. (2006) Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 4: 621-30

Lindsay J, Punekar YS, Morris J et al. (2008) Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease - modelling outcomes in active luminal and fistulizing disease in adults. Aliment Pharmacol Ther 28: 76-87

Malone DC, Waters HC, Van Den Bos J et al. (2010) A claims-based Markov model for Crohn's disease. Aliment Pharmacol Ther 32: 448-58

NHS England. Commissioning framework for biological medicines (including biosimilar medicines) 2017. Available from https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf

Peyrin-Biroulet L, Deltenre P, Ardizzone S e t al. (2009) Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. Am J Gastroenterol 104: 2089-96

Renna S, Camma C, Modesto I et al. (2008) Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. Gastroenterology 135: 1500-9

Royal College of Physicians. National clinical audit of biological therapies. UK inflammatory bowel disease (IBD) audit. Annual report September 2016. Available from https://www.rcplondon.ac.uk/projects/outputs/national-clinical-audit-biological-therapies-annual-report-2016

Rutgeerts P, Geboes K, Vantrappen G et al. (1990) Predictability of the postoperative course of Crohn's disease. Gastroenterology 89: 956-963

Royal College of Physicians. National clinical audit of biological therapies: annual report. (2016). UK inflammatory bowel disease (IBD) audit. London

Sandwell and West Birmingham Hospitals (2018) Clinical Pathology News. Available from http://www.cityassays.org.uk/downloads/Pathology%20News/pathology-news-march-2018.pdf

Shah SC, Colombel JF, Sands BE et al. (2016) Systematic review and meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Alimentary Pharmacology and Therapeutics, 43(3): 317 to 33.

Silverstein MD, Loft us EV, Sandborn WJ et al. (1999) Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology 117: 49-57

Stark RG, Reitmeir P, Leidl R, Konig HH. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. Inflammatory Bowel Diseases. 2010; 16(1):42-51

Stockport NHS Foundation Trust (2014) Request for information [online; accessed August 2018]

Wolters FL, Russel MG, Sijbrandij J et al. (2006) Phenotype at diagnosis predicts recurrence rates in Crohn's disease. Gut 55: 1124-30

E.3 Additional references

Altman, DG. and Bland, JM. (2005). Standard deviations and standard errors. Bmj, 331(7521), p.90

Collett, D. (2003). Modelling survival data in medical research, Boca raton. Florida, Chapman & Hall/CRC.

Dias, S., Welton, NJ., Sutton, AJ et al. (2011). NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials. Technical Support Document.

Dias S., Welton NJ, Sutton AJ et al. (2011) NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model. Last updated April 2012. Available from http://www.nicedsu.org.uk

Dias, S., Welton, N.J., Sutton, AJ et al. (2013). Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials. Medical Decision Making, 33(5), 641–656.

Franchini, A., Dias, S., Ades, AE et al. (2012). Accounting for correlation in mixed treatment comparisons with multi-arm trials. Research Synthesis Methods, 3, 142-160.

Turner, NL., Dias, S., Ades, AE et al. (2015). A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Statistics in medicine, 34(12), pp.2062-2080.

Woods, BS., N. Hawkins, and DA. Scott, (2010) Network meta-analysis on the log-hazard scale, combining counts and hazard ratio statistics accounting for multi-arm trials: A tutorial. BMC Medical Research Methodology, 10(1): p. 54.

Appendix F:Clinical evidence tables

Lead author and year	Title	Study details
Ardizzone (2004)	Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease.	Study type Randomised controlled trial Study details Study location Italy Study setting Single centre: tertiary care centre Study dates August 1994 to August 2001 Number of participants N=138 Duration of follow-up 24 months Intention to treat analysis Yes Sources of funding Not reported Inclusion criteria Criteria People with Crohn's disease attending a gastrointestinal unit who underwent surgery for symptomatic intestinal stenosis or occlusion were included. Diagnosis was confirmed by routine clinical, radiographic, endoscopic, and pathologic criteria. Patients had to be able to start oral nutrition and oral medication within the first 2 postoperative weeks. Exclusion criteria Criteria Contraindications for mesalamine or AZA, pre-existing hepatic disease, renal dysfunction, clinically important lung disease, systemic infection, short-bowel syndrome, presence of alcoholic stoma, history of cancer, hypersensitivity to mesalamine or AZA, erythrocyte macrocytosis, use of immunosuppressive drugs in the past 3 months, use of anti–tumour necrosis factor in past 6 months, history of corticosteroid-dependent disease pregnancy or breastfeeding.

Lead author and year	Title	Study details
		Sample characteristics Sample size Mesalazine group, n=69; Azathioprine group n=69 Mean age (SD) All participants, 38.4 years %female mesalazine group, 37%; azathioprine group, 30% Disease location Mesalazine group: small bowel only, 60.5%; colon, 9.8%; small bowel and colon, 9.8%; upper GI tract, 19.9% Azathioprine group: small bowel only, 70.4%; colon, 1.4%; small bowel and colon, 9.8%; upper GI tract, 18.4% Type of surgery not reported Indication for surgery symptomatic intestinal stenoses or occlusion Concomitant therapy Concomitant use of the following drugs was not allowed during the study: corticosteroids, anti–tumor necrosis factor methotrexate, sulfasalazine, antibiotics, nonsteroidal anti-inflammatory drugs, and other aminosalicylates. Proportion with previous surgeries mesalazine group, 53.5%; azathioprine group, 43.6% Preoperative medications mesalazine group: mesalazine, 36.6%; corticosteroids, 32.3%; immunosuppressants, 8.5%; none, 22.6% azathioprine group: mesalazine, 50.7%; corticosteroids, 25.3%; immunosuppressants, 4.2%; none, 19.8% Smoking history Mesalazine group, 39.4%; Azathioprine group, 50.7% Loss to follow-up Mesalazine group, n=4; Azathioprine group n=2 Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical relapse was defined as the presence of symptoms, variably associated with radiologic, endoscopic, and laboratory findings, with a CDAI score >200 Withdrawal due to adverse events
Armuzzi (2013)	Prevention of postoperative recurrence with	Study type Randomised controlled trial

Lead author and year	Title	Study details
	azathioprine or infliximab in patients with Crohn's disease: an open-label pilot study	Study details Study location Italy Study setting Single centre Study dates November 2007 to June 2011 Number of participants N=22 Duration of follow-up 12 months Intention to treat analysis Yes Sources of funding Not reported Inclusion criteria Criteria People who underwent ileocolonic resection and were considered at “high risk” of postoperative recurrence were enrolled. Participants were considered at “high risk” of postoperative recurrence if they had 2 or more of the following factors: young age at diagnosis (≤30 years), penetrating disease behaviour, active smoking, perianal disease at diagnosis of CD, previous surgery and less than 3 years from previous surgery. Exclusion criteria Criteria Active perianal disease, presence of stoma, adverse events during previous therapy with infliximab or azathioprine, age >70 years, surgical complications, active infectious diseases, history of cancer, renal, cardiac or hepatic failure, history of acute or chronic pancreatitis, severe leucopenia or pregnancy. Sample characteristics Sample size infliximab group, n=11; azathioprine group, n=11 Median age (IQR) infliximab group, 34 (27-37) years ; azathioprine group, 32 (21-45) years %female infliximab group, 37%; azathioprine group, 28%

Lead author and year	Title	Study details
		Median duration of disease infliximab group, 24 months; azathioprine group, 24 months Type of surgery Intestinal resection with ileocolonic stapled side-to-side anastomoses. Concomitant therapy All patients also received oral metronidazole (500 mg bid) for 2 weeks after surgery. No other Crohn's-related drugs were allowed during the study. Preoperative medications infliximab group: infliximab, 54%; azathioprine, 36% azathioprine group: infliximab, 27%; azathioprine, 18% Loss to follow-up no losses to follow-up Outcome measure(s) Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts score <2 Withdrawal due to adverse events Clinical recurrence HBI ≥ 8
Brignola (1995)	Mesalamine in the prevention of endoscopic recurrence after intestinal resection for Crohn's disease. Italian Cooperative Study Group.	Study type Randomised controlled trial Study details Study location Italy Study setting Multicenter Study dates June 1990 - December 1991 Number of participants N=87 Duration of follow-up 12 months Intention to treat analysis Yes Sources of funding

Lead author and year	Title	Study details
		Not reported Inclusion criteria Criteria So called curative resection, such as those who have undergone removal of all macroscopic disease in the ileal or ileocecal region. Exclusion criteria Criteria Patients with localisation of Crohn's disease in another region or having resection of > 100 cm. Sample characteristics Sample size Mesalamine = 44, placebo = 43 Mean age (SD) Mesalamine: 39 +/- 17 years Placebo: 34 +/- 10 years Disease location Mesalamine: 24/44 ileum and 24/44 ileum with or without cecum Placebo: 24/43 ileum and 19/44 ileum with or without cecum Mean duration of disease Mesalamine: 75 +/- 73 months Placebo: 69 +/- 54 months Proportion with previous surgeries Mesalamine: 13/44 with > 1 surgery Placebo: 11/43 with > 1 surgery Loss to follow-up Mesalamine: 1/44 Placebo: 0/43 Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical relapse defined as a worsening of the symptoms by at least 100 CDAI points and the patient's level at the previous visit and attainment of CDAI score > 150 - in these cases, either colonoscopy or barium enema was performed at the time of clinical relapse. Endoscopic assessment: Rutgeerts score Severe endoscopic recurrence: score of 3 to 4 Withdrawal due to adverse events

Lead author and year	Title	Study details
Caprilli (1994)	Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of post-operative recurrence of Crohn's disease. Gruppo Italiano per lo Studio del Colon e del Retto (GISC).	Study type Randomised controlled trial Study details Study location Italy Study setting Multicenter Study dates January 1990 - 1992 Number of participants N=110 Duration of follow-up 5 years Intention to treat analysis Yes Sources of funding Partially supported by Rracco SpA (Italy) Inclusion criteria Criteria Age between 18 and 65 years for both sexes, disease limited to the terminal ileum with or without involvement of caecum-ascending colon, resection had to be the first one and judged to be 'radical' (complete removal of the macroscopically involved intestinal segment) by the surgeon during operation, absence of skip lesions, diagnosis of Crohn's disease confirmed macroscopically and microscopically by standard criteria. Exclusion criteria Criteria -Localization of the disease to the jejunum, proximal ileum, left colon or ano-rectum, - known side-effects from sulphasalazine or salicylates; - severe diseases unrelated to Crohn's disease (for example, renal or liver dysfunction) ; treatment with drugs that may alter intestinal pH (H,-receptor antagonists, omeprazole); - pregnancy; - inability to give informed consent according to the Helsinki Declaration. Sample characteristics Sample size Mesalazine: 55 No treatment: 55

Lead author and year	Title	Study details
		Mean age (range) Mesalazine: 35.5 years (range 16 - 61) No treatment: 33.7 years (range 16 - 58) %female Mesalazine: 32% No treatment: 53.2% Mean duration of disease At symptoms: Mesalazine: 5 years (range 0 - 16) No treatment: 4.6 years (range 0 - 17) At diagnosis: Mesalazine: 3.2 years (range 0 - 12) No treatment: 2.3 years (range 0 - 10) Type of surgery Anastamosis in the: termino-terminal, termino-lateral, latero-terminal and latero-lateral sites. Indication for surgery Mesalazine group: 19/55 occulsion, 3/55 perforation, 7/55 abscess, 14/55 fistula, 6/55 intractability, 17/55 recurring sub-occlusion, 1/55 other No treatment group: 19/55 occulsion, 2/55 perforation, 9/55 abscess, 11/55 fistula, 10/55 intractability, 21/55 recurring sub-occlusion, 2/55 other Preoperative medications Mesalazine: 22/55 mesalazine, 28/55 corticosteroids, 12/55 metronidazole, 9/55 sulfasalazine No treatment: 24/55 mesalazine, 31/55 corticosteroids, 13/55 metronidazole, 12/55 sulfasalazine Duration since surgery 2 weeks Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Patients in whom CDAI was > 150, and who presented 100 points over their previous value, were considered to be symptomatic. CDAI was calculated by patients' diary cards. Endoscopic assessment: Rutgeerts score Withdrawal due to adverse events
D'Haens (2008)	Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a	Study type Randomised controlled trial Study details Study location Belgium Study setting Multicentre (performed across 2 teaching hospitals) Study dates August 1999 to September 2005

Lead author and year	Title	Study details
	controlled randomized trial.	Number of participants N=81 Duration of follow-up 12 months Intention to treat analysis Yes Sources of funding Not reported Inclusion criteria Criteria People with Crohn's disease undergoing ileal or ileocolonic resection with ileocolonic anastomosis were included. All participants had more than 1 risk factor for the development of early/severe postoperative recurrence of their Crohn's disease, based on the available literature: young age (<30 years); active smoking; corticosteroid use in the 3 months before surgery; surgery for the 2nd, 3rd, or 4th resection; and perforating disease, namely, abscess or fistula as an indication for surgery. Exclusion criteria Criteria Presence of macroscopic evidence for CD proximally or distally to the site of resection, presence of frank pancolitis or an ileorectal anastomosis (ileosigmoidal anastomosis was allowed), stoma, history for surgery for fibrostenosis without evidence of inflammatory activity, intolerance to metronidazole and/or azathioprine, low white blood cell count (<4000), alcohol or drug abuse, azathioprine use within 2 months of surgery, malignancies, ongoing infectious disease (hepatitis, tuberculosis, AIDS) with the exception of herpes simplex infection, or previous use of biologics. Sample characteristics Sample size metronidazole plus azathioprine group, n=40; metronidazole plus placebo group, n=41 Mean age (range) metronidazole plus azathioprine group, 38.8 (22-67) years; metronidazole plus placebo group, 40.0 (21-69) years %female metronidazole plus azathioprine group, 60%; metronidazole plus placebo group, 48.8% Type of surgery Ileal or ileocolonic resection with ileocolonic anastomosis Concomitant therapy Paricipants in each treatment arm recived metronidazole for 3 months postoperatively. All concomitant anti-inflammatory

Lead author and year	Title	Study details
		medications were discontinued, except for glucocorticosteroids, which were gradually tapered over 6 weeks after surgery. Antibiotics were allowed during the study for concurrent infections, but not for CD. Topical therapy for perianal CD could be continued if necessary. Proportion with previous surgeries metronidazole plus azathioprine group, 35%; metronidazole plus placebo group, 22% Preoperative medications metronidazole plus azathioprine group: azathioprine use in the past, 7% metronidazole plus placebo group: azathioprine use in the past, 5% Smoking history metronidazole plus azathioprine group, 32.5%; metronidazole plus placebo group, 41.5% Loss to follow-up metronidazole plus azathioprine group, 20%; metronidazole plus placebo group, 29.3% Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical relapse was defined as a CDAI score >250. Thus it is considered that remission would be categorised as scores below this threshold. Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts' score Withdrawal due to adverse events
Ewe (1989)	Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: a multicenter trial.	Study type Randomised controlled trial Study details Study location Germany Study setting Multicentre (performed across 16 surgical departments) Study dates not reported Number of participants N=232 Duration of follow-up 36 months Intention to treat analysis

Lead author and year	Title	Study details
		Yes Sources of funding Not reported Inclusion criteria Criteria People having resection for Crohn's disease (radical or non-radical resection as customary in each participating centre) were included. No macroscopically inflamed intestine was allowed to be left neither locally at the site of operation nor elsewhere in the gastrointestinal tract (skip lesions). The diagnosis of Crohn's had to be confirmed macroscopically and microscopically. Exclusion criteria Criteria Refusal or inability to give informed consent, questionable ability, or severe disease. Sample characteristics Sample size sulfasalazine group, n=111; placebo group, n=121 Median age (Range) sulfasalazine group, 32 (16-66) years; placebo group, 30 (15-62 years) %female sulfasalazine group, 56.8%; placebo group, 46.3% Disease location sulfasalazine group: ileium and colon, 91%; ileum only, 1%; colon only, 8% placebo group: ileium and colon, 90%; ileum only, 3%; colon only, 7% Concomitant therapy not reported Outcome measure(s) Crohn's Disease Activity Index (CDAI) score CDAI thresholds for remission were not sepcified.
Ewe (1999)	Low-dose budesonide treatment for prevention of	Study type Randomised controlled trial

Lead author and year	Title	Study details
	postoperative recurrence of Crohn's disease: a multicentre randomized placebo-controlled trial. German Budesonide Study Group.	Study details Study location Germany Study setting Multicentre (performed across 3 medical centres) Study dates July 1992 to April 1994 Number of participants N=83 Duration of follow-up up to 24 months Intention to treat analysis Yes Sources of funding Not reported Inclusion criteria Criteria People who underwent resection for ileal, ileo-colonic or colonic Crohn's diseasee and had an anastomosis which was accessible to colonoscopy were included. Exclusion criteria Criteria Lack of compliance, intraoperative ileostomy, or error in diagnosis. Sample characteristics Sample size budesonide group, n=43; placebo group, n=40 Mean age (SD) budesonide group, 35 (12) years ; placebo group, 33 (9) years %female budesonide group, 51.2%; placebo group, 60% Disease location budesonide group: ileium and colon, 60.5%; ileum only, 27.9%; colon only, 11.6% placebo group: ileium and colon, 60%; ileum only, 22.5%; colon only, 17.5% Mean duration of disease

Lead author and year	Title	Study details
		budesonide group, 100 months; placebo group, 81 months Concomitant therapy No other drugs used in the treatment of Crohn's disease were allowed Proportion with previous surgeries budesonide group, 58.1%; placebo group, 67.5% Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical remission was defined as a CDAI score <150 Withdrawal due to adverse events
Hanauer (2004)	Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial.	Study type Randomised controlled trial Study details Study location USA Study setting Multicenre (performed across 5 medical centres) Study dates 1992 to 1996 Number of participants N=131 Duration of follow-up 24 months Intention to treat analysis Yes Sources of funding The study was supported by a research grant from the Crohn’s and Colitis Foundation of America and the David and Reva Logan GI Research Center at the University of Chicago. Study drugs and matching placebo were provided by Marion Merrill Dow (mesalamine) and Burroughs Wellcome (6-mercaptopurine). Inclusion criteria Criteria People with Crohn's disease undergoing first or subsequent ileocolic resection with a primary anastomosis for disease

Lead author and year	Title	Study details
		confined to the ileum and adjacent colon were eligible. Exclusion criteria Criteria Patients were excluded if there was evidence of gross Crohn's disease at the operative margins or in proximal or distal segments of intestine (excluding perianal disease) at the time of surgery or at pathologic examination. Sample characteristics Sample size mesalazine group, n=44; mercaptopurine group, n=47; placebo group, n=40 %female mesalazine group, 57%; mercaptopurine group, n=51%; placebo group, 55% Mean duration of disease mesalazine group, 120 months; mercaptopurine group, 113 months; placebo group, 127 months Indication for surgery % perforating - mesalazine group, 45%; mercaptopurine group, 33%; placebo group, 32% Concomitant therapy No concurrent treatment for Crohn's disease, aside from topical therapy for perianal disease, was allowed during the duration of the trial. Preoperative medications Presurgical therapy, including aminosalicylates, antibiotics, or immunomodulators, was discontinued before surgical resection and was not allowed during the postoperative trial. Outcome measure(s) Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts score Clinical assessment Clinical relapse was defined by a bespoke clinical recurrence grading scale Withdrawal due to adverse events
Hellers (1999)	Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. The	Study type Randomised controlled trial Study details Study location Belgium, Denmark, France, Germany, Italy, the Netherlands, the United Kingdom, and Sweden

Lead author and year	Title	Study details
	IOIBD Budesonide Study Group.	Study setting Multicentre (performed across 13 medical centres) Study dates February 1992 to August 1993 Number of participants N=129 Duration of follow-up 12 months Intention to treat analysis Yes Sources of funding Not reported Inclusion criteria Criteria Patients scheduled for resectional surgery for ileocolonic Crohn's disease were included. Exclusion criteria Criteria Patients who had a septic complication, such as abscess or fistula, or who had previously had more than 100 cm of the terminal ileum resected were excluded. Sample characteristics Sample size budesonide group, n=63; placebo group, n=66 Mean age (range) budesonide group, 34 (20-76) years; placebo group, 36 (17-81) years %female budesonide group, 44.4%; placebo group, 59.1% Concomitant therapy Use of systemic glucocorticoids had to be discontinued within 30 days of surgery. No other concurrent medication for the treatment of Crohn's disease was allowed. Proportion with previous surgeries budesonide group: obstruction, 57.1%;disease activity, 34.9% placebo group: obstruction, 63.6%; disease activity, 28.8%

Lead author and year	Title	Study details
		Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Recurrence was defined as a CDAI score >200. Thus it is considered that remission would be categorised as scores below this threshold. Endoscopic assessment: Rutgeerts score Remission was defined as a Rutgeerts score Withdrawal due to adverse events
Lochs (2000)	Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI.	Study type Randomised controlled trial Study details Study location Austria, Denmark, Germany, Norway, Sweden and Switzerland. Study setting Multicenter Study dates 1992 - 1996 Number of participants N=318 Duration of follow-up 18 months Intention to treat analysis Yes Inclusion criteria Criteria 18 - 70 years who underwent a resective surgical procedure (radical or nonradical) for a Crohn's disease specific lesion at 1 of the participating centers. Specific inclusion criteria were: - A diagnosis of CD established by endoscopic, histological and and/or radiological criteria at least 6 months before surgery; - evaluation of disease location by a complete investigation of the gastrointestinal tract (gastroscopy, colonoscopy, and small bowel radiography) within a maximum of 1 year before the index surgery; - and ability to start oral nutrition (and, thus, oral medication) within the first 10 postoperative days. Exclusion criteria Criteria

Lead author and year	Title	Study details
		- contraindications for use of mesalamine; - pregnancy or intention of pregnancy within the next 18 months; nursing; short bowel syndrome; - clinically significant lactase deficiency; - any severe additional disease; diagnosis of primary sclerosing cholangitis; - presence of an ileocolonic stoma; - more than 3 surgeries preceding the index surgery; - and failure to obtain informed consent Sample characteristics Sample size Mesalamine: 152 Placebo: 166 Mean age (SD) Mesalamine: 33.4 (10) Placebo: 33.8 (10.2) %female Mesalamine: 53% Placebo: 49% Disease location Mesalamine: 36.2% small bowel only, 59.2% small bowel and colon, 4.6% colon only Placebo: 41.6% small bowel only, 53.6% small bowel and colon, 8% colon only Indication for surgery Mesalamine: Fistula N=1, stenosis N=16, inflammation N=9, fistula + stenosis N=5, Fistula + inflammation N=12, stenosis + inflammation N=78, Fistula + stenosis + inflammation N=28, no information N=3 Placebo: Fistula N=1, stenosis N=16, inflammation N=20, fistula + stenosis N=4, Fistula + inflammation N=12, stenosis + inflammation N=77, Fistula + stenosis + inflammation N=34, no information N=2 Duration since surgery 10 days Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical relapse as defined by 1 of the following: increase in CDAI above 250; increase in CDAI above 200 but by a minimum of 60 points over the lowest postoperative value for 2 consecutive weeks (this definition was used to avoid that temporary deteriorations with slight increases of the CDAI were improperly counted as relapses); indication for surgery; development of a new fistula; and occurrence of a septic complication. Endoscopic assessment: Rutgeerts score < i2
Lopez-Sanroman (2017)	Adalimumab vs Azathioprine in the Prevention of Postoperative	Study type Randomised controlled trial

Lead author and year	Title	Study details
	Crohn's Disease Recurrence. A GETECCU Randomised Trial	Study details Study location Spain Study setting Multicentre (unclear how many centres were involved) Study dates January 2012 to January 2015 Number of participants N=91 Duration of follow-up 12 months Intention to treat analysis Yes Sources of funding This work was supported by an unrestricted grant from AbbVie. The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decisions concerning publication. Inclusion criteria Criteria Patients aged 18 to 70 years with a confirmed diagnosis of Crohn's disease who were undergoing elective ileocolonic or ileocaecal resection were eligible for inclusion. Exclusion criteria Criteria Intolerance to azathioprine or adalimumab, previous failure of either drug in the prevention of postoperative recurrence, postsurgical stoma, resection for short indolent stenosis, anastomosis that was inaccessible to standard endoscopy, local macroscopic disease after resection, contraindications to anti TNFα therapy. Sample characteristics Sample size met. plus azathioprine group, n=39; met plus adalimumab group, n=45 Median age (IQR) met. plus azathioprine group, 37 (31-47) years ; met plus adalimumab group, 35 (30-40) years %female met. plus azathioprine group, 41%; met plus adalimumab group, 57.8% Mean duration of disease

Lead author and year	Title	Study details
		met. plus azathioprine group, 7.3 years; met plus adalimumab group, 8.1 years Concomitant therapy All participants recieved metronidazole for 3 months after surgery Proportion with previous surgeries met. plus azathioprine group, 7.7%; met plus adalimumab group, 6.7% Preoperative medications met. plus azathioprine group - glucocorticoids, 97.4%; immunosuppressants, 93.3%; anti TNFα, 53.8% met plus adalimumab group, - glucocorticoids, 93.3%; immunosuppressants, 77.8%%; anti TNFα, 62.2% Smoking history met. plus azathioprine group, 23.1%; met plus adalimumab group, 24.4% Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Relapse was defined as a CDAI score >200. Thus it is considered that remission would be categorised as scores below this threshold. Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts score Hospitalisation
Manosa (2013)	Addition of Metronidazole to Azathioprine for the Prevention of Postoperative Recurrence of Crohn's Disease: A Randomized, Double-Blind, Placebo-Controlled Trial	Study type Randomised controlled trial Study details Study location *Spain* Study setting *Multicenter* Study dates *January 2004 to January 2010* Number of participants *N=50* Duration of follow-up *12 months maximum.*

Lead author and year	Title	Study details
		Intention to treat analysis *Yes* Inclusion criteria Criteria *All consecutive adult patients with CD undergoing ileal or ileocolic resection with ileocolic or ileorectal anastomosis.* Exclusion criteria Criteria *(1) Intolerance or known allergy to the study drugs; (2) erythrocyte thiopurine methyltransferase activity ,5 U/mL red blood cells; (3) previous treatment with thiopurines for the same indication (prevention of postoperative recurrence); (4) antecedents of malignancy; (5) ongoing infectious disease; (6) pregnancy or a desire to become pregnant; (7) intolerance to oral intake; and (8) use of any investigational drug in the preceding 6 months.* Sample characteristics Sample size *Metronidazole (3 months) + AZA: 25 Placebo + AZA: 25* Mean age (SD) *Metronidazole (3 months) + AZA: 36.2 (12) Placebo + AZA:: 34.52 (8)* %female *Metronidazole: 52% Placebo: 40%* Disease location *Location (ileal/colonic/ileocolic): Metronidazole (3 months) + AZA:: 17/1/7 Placebo + AZA:: 15/0/10* Type of surgery *Ileal or ileocolic resection with ileocolic or ileorectal anastomosis.* Additional stricturoplasties *Metronidazole (3 months) + AZA:: 12% Placebo + AZA: 8%* Duration since surgery

Lead author and year	Title	Study details
		Mean days (SD) Metronidazole: 12.6 (9) Placebo: 10.6 (4.7) Outcome measure(s) Ileocolonoscopy (to look for recurrence) *At 6 and 12 months. Patients who developed clinical or endoscopic recurrence before the 12-month endoscopic exploration were regarded as treatment failures and did not undergo further evaluation.* Adverse events Patients withdrawn from study
Mowat (2016)	Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial	Study details Study location UK Study setting Multicentre (performed across 29 secondary and tertiary UK hospitals) Study dates Number of participants N=240 Duration of follow-up 36 months Intention to treat analysis Yes Sources of funding The srudy was funded by the Medical Research Council. Inclusion criteria Criteria Patients aged at least 16 years (Scotland) or 18 years (England and Wales) who had a diagnosis of Crohn’s disease and an ileocolic or small bowel resection within the preceding 3 months were eligible for inclusion. Exclusion criteria Criteria Residual active Crohn’s disease present after surgery, known intolerance or hypersensitivity to thiopurines, known need

Lead author and year	Title	Study details
		for further surgery, strictureplasty alone, formation of a stoma, active or untreated malignancy, absent thiopurine methyltransferase activity, substantial abnormalities of liver function tests or pregnancy. Sample characteristics Sample size mercaptopurine group, n=128; placebo group, n=112 Mean age (SD) mercaptopurine group, 39.2 (12.8) years; placebo group, 38.2 (13.4) years Disease location mercaptopurine group: ileocolonic, 55%; ileal, 42%; colonic, 3% placebo group: ileocolonic, 63%; ileal, 35%; colonic, 2% Duration of disease ≤1 year mercaptopurine group, 29%; placebo group, 37% Mean duration of disease mercaptopurine group, 7.7 years; placebo group, 7.6 years Concomitant therapy not reported Proportion with previous surgeries mercaptopurine group, 36%; placebo group, 25% Preoperative medications mercaptopurine group: azatioprine, 63%; infliximab, 16%; methotrexate, 6%; corticosteroids, 76% placebo group: azatioprine, 42%; infliximab, 13%; methotrexate, 6%; corticosteroids, 71% Smoking history mercaptopurine group, 23%; placebo group, 23% Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical relapse at was defined as CDAI >150, a 100 point increase from baseline and the need for anti-inflammatory rescue treatment. Endoscopic assessment: Rutgeerts score Recurrence was defined as a Rutgeerts score of at least i2. Adverse events/serious adverse events Withdrawal due to adverse events
Regueiro (2009)	Infliximab prevents Crohn's disease	Study type Randomised controlled trial

Lead author and year	Title	Study details
	recurrence after ileal resection	Study details Study location USA Study setting Single centre Study dates 2005 to 2007 Number of participants N=24 Duration of follow-up 12 months Intention to treat analysis Yes Sources of funding This work was funded in part by an unrestricted grant from the manufacturer. Inclusion criteria Criteria Patients with ileal or ileocolonic Crohn's disease undergoing resection of macroscopically diseased bowel with anastomosis between normal ileum and colon (ie, ileocolonic anastomosis) were included. Exclusion criteria Criteria More than 10 years of Crohn's disease requiring first resective surgery for short (<10 cm) fibrostenotic stricture, macroscopically active disease not resected at the time of surgery, presence of a stoma, and prior severe reactions to infliximab. Sample characteristics Sample size infliximab group, n=11; placebo group, n=13 Median age (Range) infliximab group, 43 (28-48) years; placebo group, 32 (26-45) years %female infliximab group, 45.5%; placebo group, 23.1% Disease location infliximab group:imeum and colon, 81.8%; ileum only, 18.2% placebo group: imeum and colon, 76.9%; ileum only, 23.1%

Lead author and year	Title	Study details
		Median duration of disease infliximab group, 13 years; placebo group, 9 years Concomitant therapy infliximab group: immunomodulator use, 36.4% placebo group: immunomodulator use, 53.8 Proportion with previous surgeries infliximab group, 36.4%; placebo group, 30.8% Smoking history infliximab group, 45.5%; placebo group, 7.7% Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Remission was defined as a CDAI score <150 Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts score Withdrawal due to adverse events Hospitalisation
Regueiro (2016)	Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection	Study type Randomised controlled trial Study details Study location Global Study setting Multicentre (performed across 104 sites) Study dates November 2010 to May 2012 Number of participants N=297 Duration of follow-up 26 months Intention to treat analysis Yes (for some outomes) Sources of funding No details relating to funding were reported. However, some investigators recieved consulting fees from various

Lead author and year	Title	Study details
		pharmaceutical manufaturers. Inclusion criteria Criteria People 18 years old with a confirmed diagnosis of Crohn's disease who had undergone ileocolonic resection with ileocolonic anastomosis. Patients were also required to have a baseline CDAI score <200 and at least 1 of the following risk factors for disease recurrence: qualifying surgery that was their second intra abdominal resection within 10 years; third or more intra-abdominal resection; resection for a penetrating CD complication (eg, abscess or fistula); a history of perianal istulising CD, provided the event had not occurred within 3 months; or smoking 10 or more cigarettes per day for the past year. Exclusion criteria Not reported Sample characteristics Sample size infliximab group, n=147; placebo group, n=150 Mean age (SD) infliximab group, 37.1 (13.5) years; placebo group, 35.4 (12.41) years %female infliximab group, 46%; placebo group, 47.6% Mean duration of disease infliximab group, 8.4 (8.7) years; placebo group, 6.4 (7.5) years Concomitant therapy Patients receiving oral mesalamine or immunosuppressives pre-surgery could continue treatment with maintenance of stable doses after resection. Patients not receiving these agents pre-surgery could not receive them post-surgery Initiation of corticosteroids or antibiotics for CD treatment was prohibited. Preoperative medications infliximab group: anti-TNF, 25.3%; adlimumab, 12.8%; infliximab, 11.1%; certolizumab, 1.0% placebo group: anti-TNF, 20.0%; adlimumab, 11.3%; infliximab, 10.0%; certolizumab, 0% Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Relapse was defined as a CDAI score >200. Thus it is considered that remission would be categorised as scores below this threshold. Endoscopic assessment: Rutgeerts score

Lead author and year	Title	Study details
		Endoscopic remission was defined as a Rutgeerts score Adverse events/serious adverse events Withdrawal due to adverse events Infection Hospitalisation
Rutgeerts (1995)	Controlled Trial of Metronidazole Treatment for Prevention of Crohn's Recurrence After Ileal Resection	Study type Randomised controlled trial Study details Study location *Belgium* Study setting *Single centre* Study dates *December 1988 to January 1991* Number of participants *N=60* Duration of follow-up *Up to 3 years* Intention to treat analysis *Yes* Sources of funding *No details relating to funding were reported.* Inclusion criteria Criteria *People who underwent a curative resection of the terminal ileum and partial colectomy with ileocolonic resection for complications of ileal Crohn's disease. Patients with first resection as well as patients who had undergone prior resections were included.*

Lead author and year	Title	Study details
		Exclusion criteria *Patients who underwent a two-step procedure were not included in the study.* Sample characteristics Sample size *Metronidazole, n=30; placebo group, n=30* Mean age (SD) *Metronidazole, 33 (10.3) years; placebo group, 37 (13.8) years* %female *Not provided* Mean duration of disease *Metronidazole, 9 years; placebo group, 10 years* Concomitant therapy *No other drugs were allowed except for antidiarrheic drugs. In patients who had received corticosteroids before surgery, the corticosteroids were tapered and stopped within 4 weeks after surgery.* Preoperative medications *Metronidazole group: glucocorticosteroids at the time of surgery = 14; broad-spectrum antibiotics at the time of surgery = 15; previous immunosuppressive therapy = 0; previous treatment with metronidazole in the course of disease = 6; clinical response to metronidazole during previous therapy = 5. Placebo group: glucocorticosteroids at the time of surgery = 15; broad-spectrum antibiotics at the time of surgery = 17; previous immunosuppressive therapy = 0; previous treatment with metronidazole in the course of disease = 7; clinical response to metronidazole during previous therapy = 5* Outcome measure(s) Endoscopic assessment: *The end points of the study were first the presence and the severity of endoscopic and histological recurrent lesions in the neoterminal ileum at 3 months as well as the status of the neoterminal ileum at 3 years after resection.* Clinical recurrence: *The second end point was the clinical recurrence of the disease at 1, 2, and 3 years after surgery.*
Tursi (2014)	Comparison of the effectiveness of infliximab and	Study type Randomised controlled trial

Lead author and year	Title	Study details
	adalimumab in preventing postoperative recurrence in patients with Crohn's disease: an open-label, pilot study	Study details Study location Italy Study setting Not reported Study dates January 2010 to May 2013 Number of participants N=20 Duration of follow-up 12 months Intention to treat analysis Not reported Inclusion criteria Criteria Consecutive CD patients who underwent curative ileocolonic resection and were considered to be at high risk of postoperative recurrence were enrolled. Patients were considered at ‘‘high risk’’ for postoperative recurrence if they had 2 or more of the following risk factors: - young age at diagnosis (up to 30 years), - penetrating disease, - active smoking, - perianal disease at diagnosis and - previous surgery and up to 3 years from previous surgery. Exclusion criteria Criteria Active perianal disease, the presence of stoma, adverse events during previous therapy with IFX or AZA, age greather than 70 years, surgical complications, active infectious diseases, history of cancer, renal, cardiac or hepatic failure, history of acute or chronic pancreatitis, severe leucopenia (WBC<3,000 lu/mL, lymphocyte count <1,000 lu/mL) and pregnancy. Sample characteristics Sample size INF=10 ADA=10 Median age (Range) INF= 30.5 (20-33) ADA=34.5 (22-39) Median duration of disease INF= 48 months ADA=48 months Smoking history

Lead author and year	Title	Study details
		INF= 3/10 ADA= 2/10 Outcome measure(s) Endoscopic assessment: Rutgeerts score Recurrence is score of 2 or more. Harvey Bradshaw Index (HBI) >= 8
Wenckert (1978)	The long-term prophylactic effect of salazosulphapyridine (Salazopyrin) in primarily resected patients with Crohn's disease. A controlled double-blind trial.	Study type Randomised controlled trial Study details Study location Denmark and Sweden Study setting Multicentre (performed across 3 centres) Study dates Not reported Number of participants N=66 Duration of follow-up 18 months Intention to treat analysis No Sources of funding Not reported Inclusion criteria Criteria Patients with Crohn's disease of the small and/or large bowel which had been macroscopically resected, at the first surgical intervention for Crohn's disease. In all participants, histological examination had shown granulomas and/or transmural, focal-lymphocytic inflammation. Exclusion criteria Criteria Treatment by by-pass, if ESR levels did not return to normal levels within 6 weeks after surgery, allergies to

Lead author and year	Title	Study details
		sulphonamides or acetylsalicylic acid, considered non-cooperative, or receiving corticosteroids or immunosuppresive drugs. Sample characteristics Sample size Not reported Mean age (SD) Not reported %female 50% across the whole study (group specific proportions were not reported) Outcome measure(s) Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts score Clinical assessment Relapse was categorised by the presence of symptoms (fever, diarrhoea etc.) and not on an index
Yoshida (2012)	Scheduled infliximab monotherapy to prevent recurrence of Crohn's disease following ileocolic or ileal resection: a 3-year prospective randomized open trial	Study type Randomised controlled trial Study details Study location Japan Study setting Single centre Study dates June 2007 to February 2011 Number of participants N=31 Duration of follow-up 36 months Intention to treat analysis Yes Sources of funding The study was supported by a grant from the Japan Ministry of Health, Labour and Welfare.

Lead author and year	Title	Study details
		Inclusion criteria Criteria Men and women between 12 and 65 years with ileal or ileocolic Crohn's disease were eligible rif they had undergone macroscopic disease resection with anastomoses, which were side-to-side and stapled. Surgery had to be performed within 4 weeks of enrolment. Exclusion criteria Criteria Concomitant azathioprine or 6-mercaptopurine that had started within 8 weeks prior to study comencement, concomitant prednisolone, active infection, macroscopically active disease missed during surgery or the presence of abscess, confirmed tuberculosis, or a history of intolerance to infiximab. Sample characteristics Sample size infliximab group, n=15; control group, n=16 Mean age (SD) infliximab group, 36.9 (11.6) years; control group, 32.8 (10.2) years %female infliximab group, 26.7%; control group, 25% Disease location infliximab group: ileum, 26.7%; ileum and colon, 73.3% control group: ileum, 25%; ileum and colon, 75% Mean duration of disease infliximab group, 11.6 (8.8) years; control group, 9.2 (7.1) years Indication for surgery infliximab group: obstruction, 80%; abscess, 87.5% control group: obstruction, 20%; abscess, 12.5% Concomitant therapy Oral mesalazine (pentasa) given to patients in both arms at same mean dose of 2.25 g/day Elemental diet (if reported) less than 1200 kcal/day. Proportion with previous surgeries infliximab group, 26.7%; control group, 37.5% Postoperative medications infliximab group: elemental diet, 46.7%; mesalazine, 100% control group, elemental diet, 81.3%; mesalazine, 100% Smoking history infliximab group, 80%; control group, 81.3%

Lead author and year	Title	Study details
		Outcome measure(s) Crohn's Disease Activity Index (CDAI) score Clinical remission was defined as a CDAI score <150 Endoscopic assessment: Rutgeerts score Endoscopic remission was defined as a Rutgeerts score Adverse events/serious adverse events Withdrawal due to adverse events

F.1 Risk of bias assessment

Study	Random sequence	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Support for judgment	ROB overall
Ardizzone 2004	Low	Unclear	HIGH	Unclear	Low	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for objective outcomes.
Armuzzi 2013	Low	Unclear	High	High	Low	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for objective outcomes.
Brignola 1995	Low	Unclear	Low	Low	Low	Low	Low	None identified	LOW
Caprilli 1994	Low	Unclear	High	High	Low	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for

Study	Random sequence	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Support for judgment	ROB overall
									objective outcomes.
D'Haens 2008	Low	Low	Unclear	Low	High	Low	Low	None identified	Moderate
Ewe 1989	Unclear	Unclear	Low	Unclear	Low	Low	Low	None identified	Low
Ewe 1999	Low	Unclear	Low	Unclear	High	Low	Low	None identified	Moderate
Hanauer 2004	Low	Low	Low	Low	High	Low	Low	None identified	Moderate
Hellers 1999	Low	Unclear	Low	Unclear	High	Low	Low	None identified	Moderate
Lochs 2000	Low	Low	Low	Low	Low	Low	Low	None identified	Low
Lopez-Sanroman	Low	Low	High	Low	High	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for objective outcomes.
Manosa 2013	Low	Low	Low	Unclear	Low	Low	Low	None identified	Low
McCleod 1995	Low	Unclear	Low	Low	Low	Low	Unclear	In March 1991, Rowasa production was discontinued and consequentially replaced with an equivalent dose of Salofalk (for the treatment arm).	Low

Study	Random sequence	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Support for judgment	ROB overall
Mowat 2016	Low	Low	Low	Low	Low	Low	Unclear	"There was low patient recruitment (only one or two patients) at several centres, which resulted in only one treatment being assigned at these centres, which created the imbalance in recruitment numbers between treatment groups."	Low
Regueiro 2016	Low	Unclear	Low	Unclear	High	Low	High	Medium disease duration at baseline was longer in infliximab (median = 6.49, mean= 8.38 years) than in placebo group (median =3.32, mean = 6.39 years).	Moderate

Study	Random sequence	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Support for judgment	ROB overall
Rugueiro 2009	Low	Unclear	Low	Low	Low	Low	High	Noted some significant baseline characteristic differences between groups: The infliximab group had significantly more active smokers (45.5% vs 7.7%), significantly higher median baseline ERS (40 vs 11), significantly higher median CRP conventrations (0.5 vs .01), a trend for less concomitant immunomodulators use (36.4 vs 53.8%) and mesalamine use (9.1% vs 30.8%).	Moderate
Rutgeerts 1995	Low	Unclear	Low	Low	High	Low	Low	None identified	Moderate
Savarino 2013	Low	Low	High	Low	Low	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for objective outcomes.
Tursi 2013	Low	Unclear	High	High	Low	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for objective outcomes.

Study	Random sequence	Allocation concealment	Blinding of participant/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Support for judgment	ROB overall
Wenckert 1978	Low	Unclear	Low	Unclear	Low	Low	Low	None identified	Low
Yoshida 2012	Low	Low	High	Low	Low	Low	Low	None identified	High (unblinded) for subjective outcomes, Moderate for objective outcomes.

Appendix G: Forest plots

Mesalazine versus placebo

Clinical remission (author defined)

Figure 8: Clinical remission at 12 months

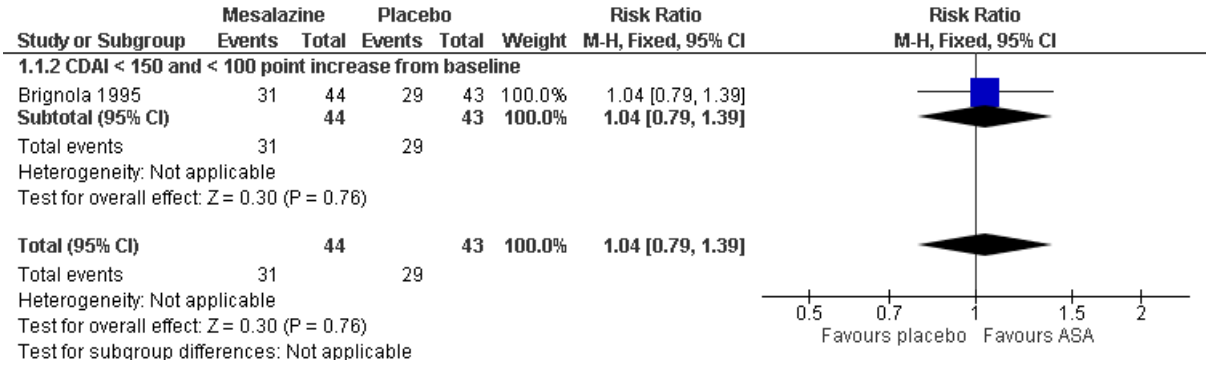


Figure 9: Clinical remission at 18 months

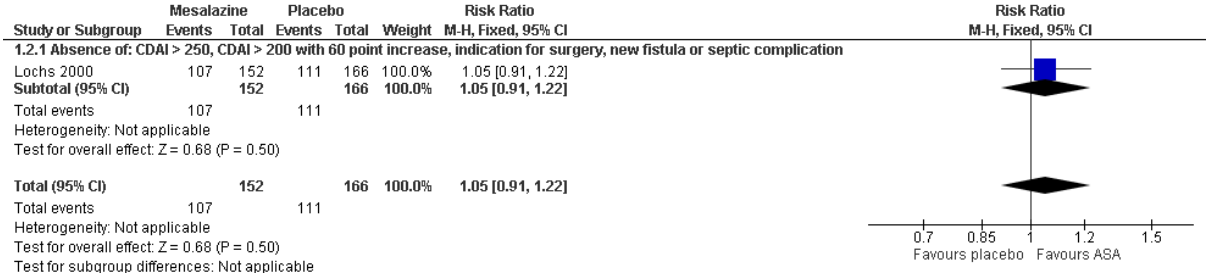
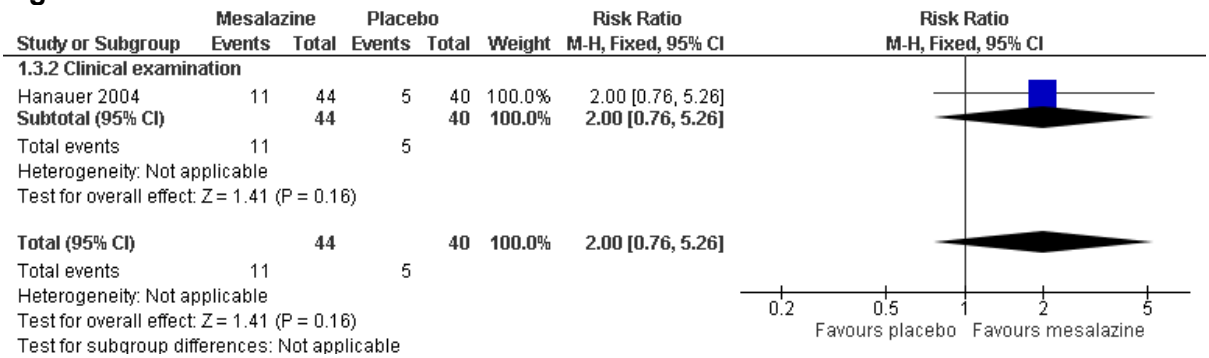


Figure 10: Clinical remission at 24 months



Endoscopic remission

Figure 11: Endoscopic remission at 12 months (Rutgeerts' score = < i2)

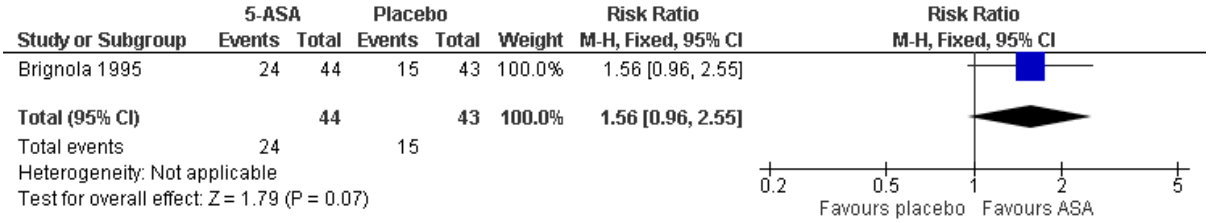


Figure 12: Endoscopic remission at 18 months (Rutgeerts' score = < i2)

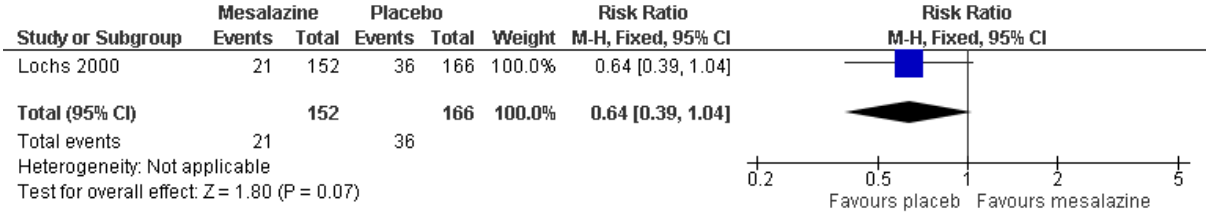
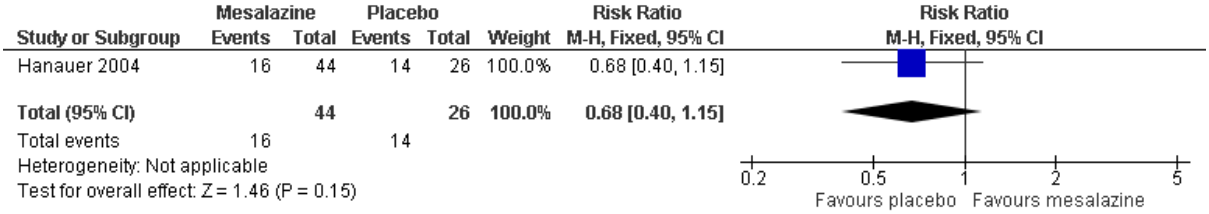
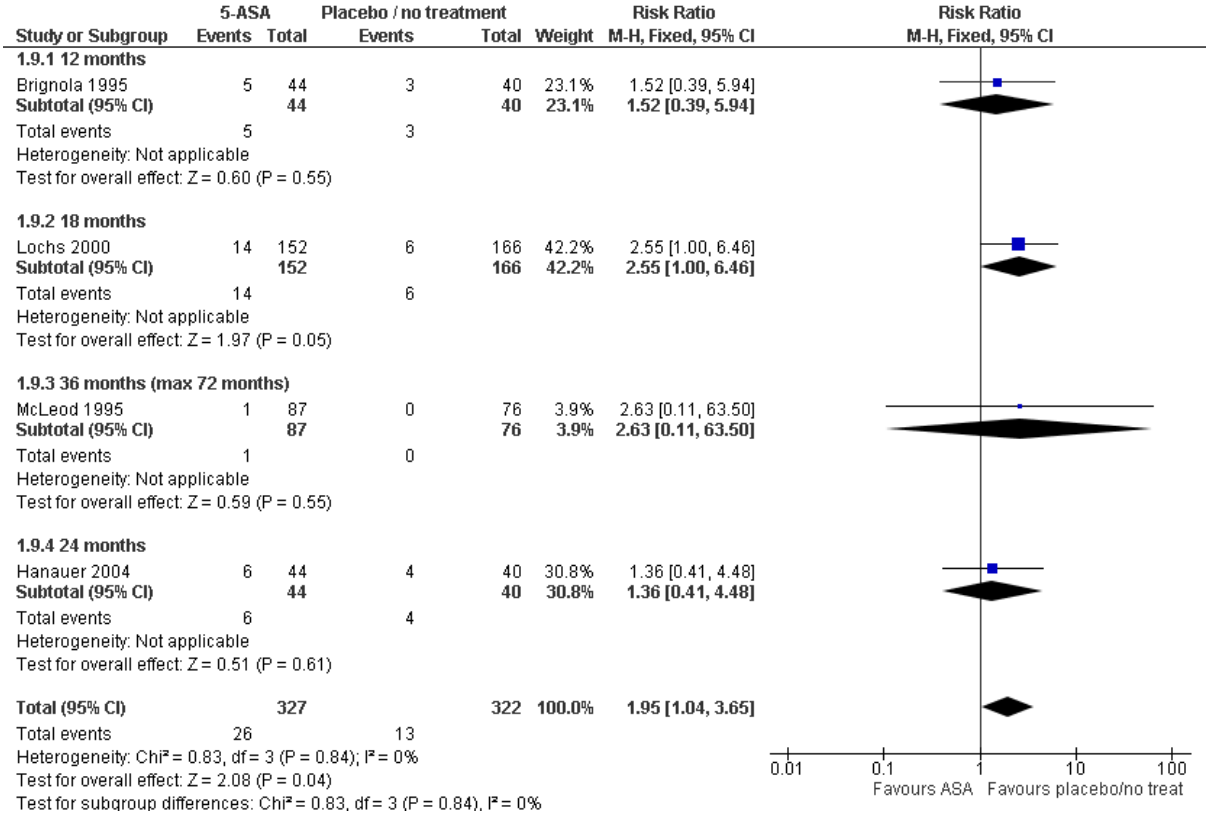


Figure 13: Endoscopic remission at 24 months (Rutgeerts' score = < i2)



Withdrawal due to adverse events

Figure 14: Withdrawal due to adverse events



Mesalazine versus no treatment

Clinical remission

Figure 15: Clinical remission at 12 months

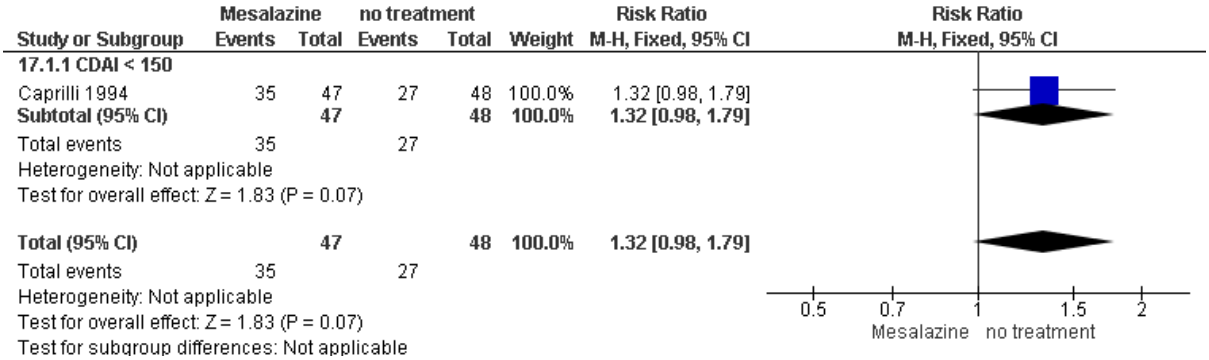
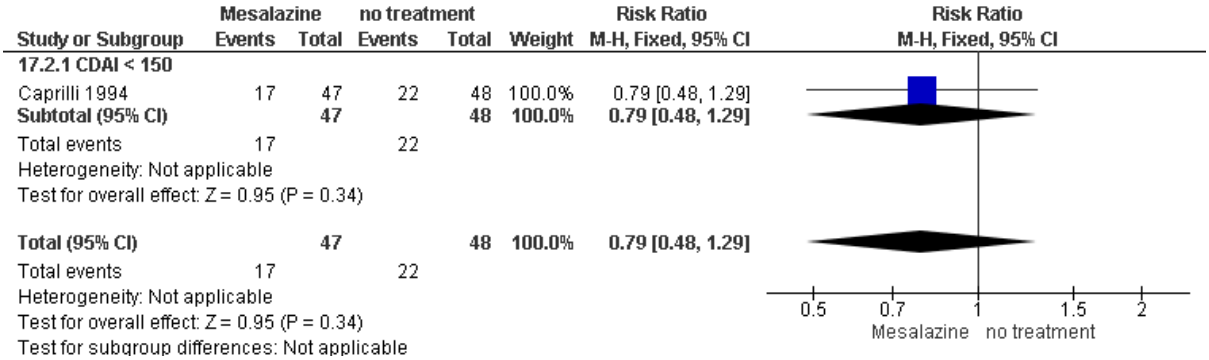


Figure 16: Clinical remission at 24 months



Endoscopic remission

Figure 17: Endoscopic remission at 12 months (Rutgeerts' score = i0)

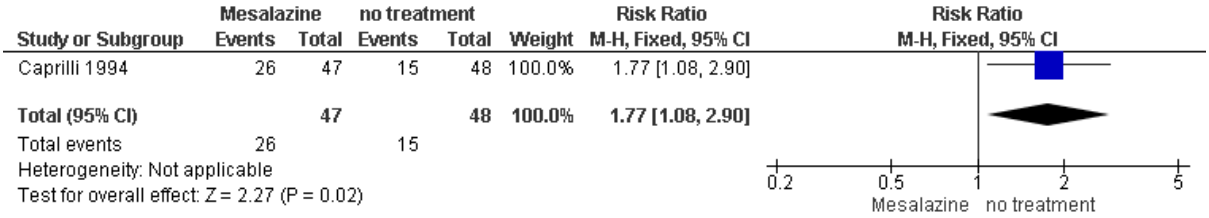
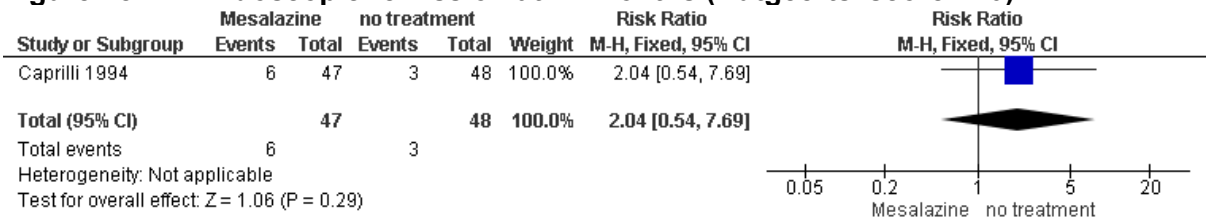


Figure 18: Endoscopic remission at 24 months (Rutgeerts' score = i0)



Withdrawal due to adverse events

Figure 19: Withdrawal due to adverse events at 12 months

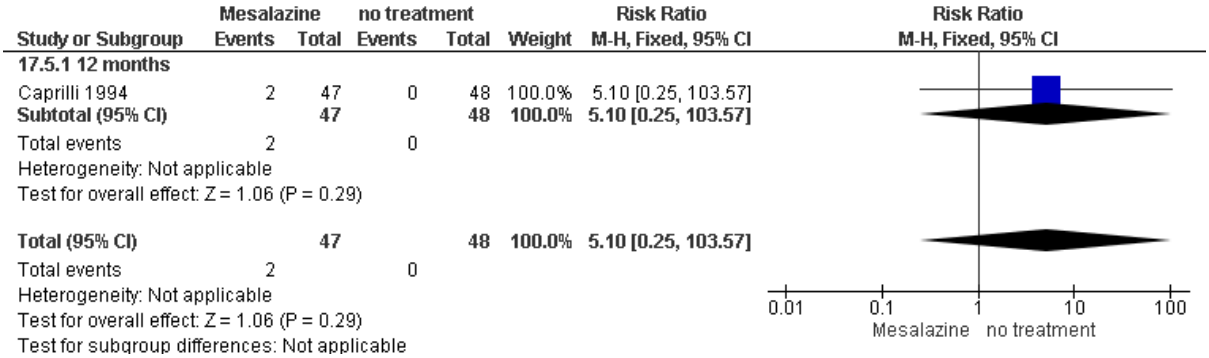
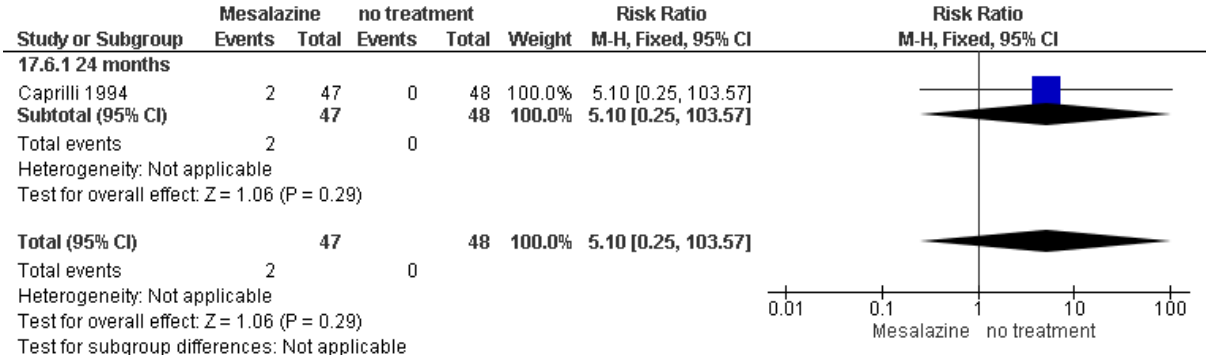


Figure 20: Withdrawal due to adverse events at 24 months



Sulfasalazine versus placebo

Clinical remission

Figure 21: Clinical remission at 12 months

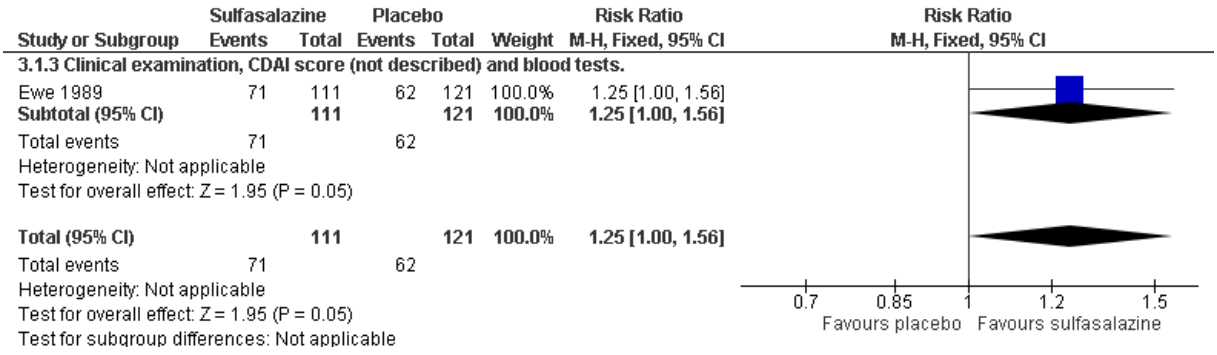


Figure 22: Clinical remission at 18 months

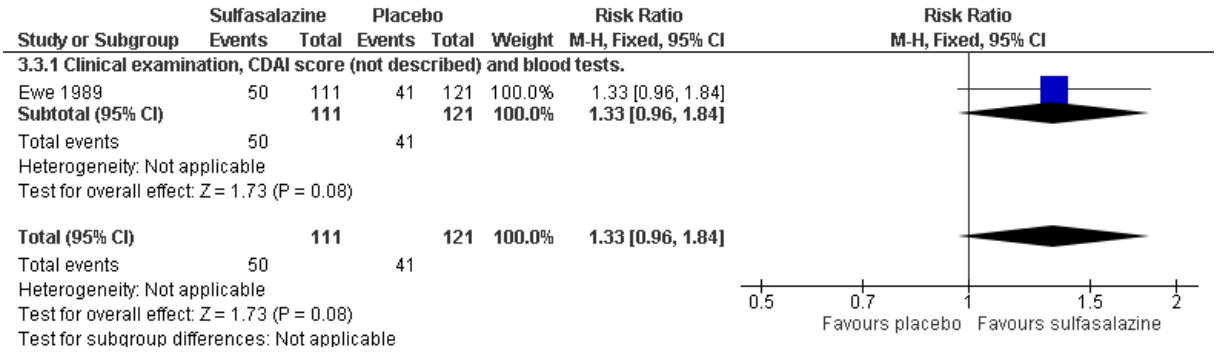
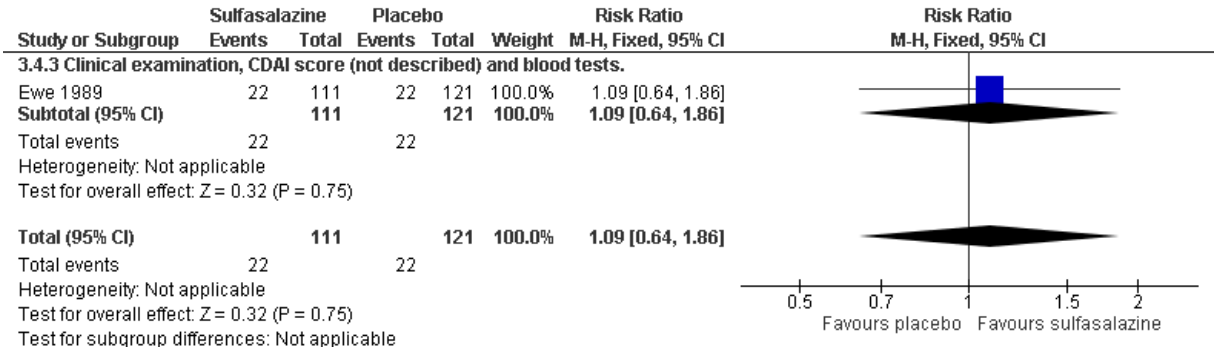


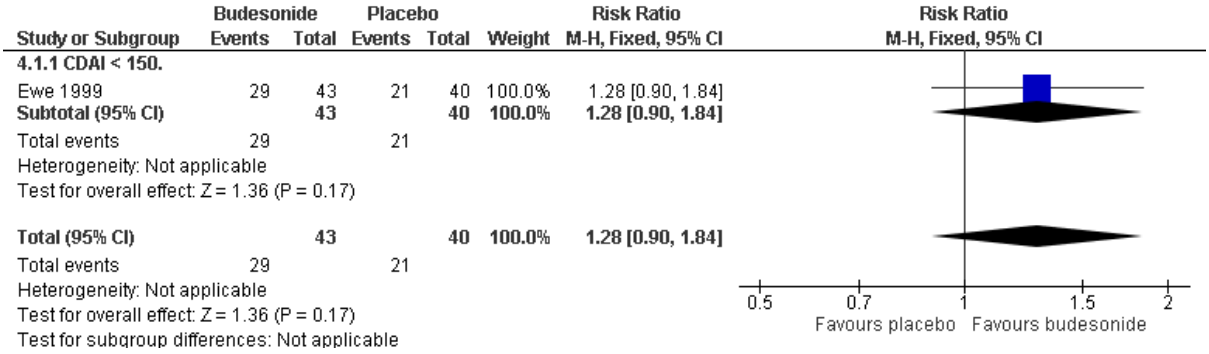
Figure 23: Clinical remission at 24 months



Budesonide versus placebo

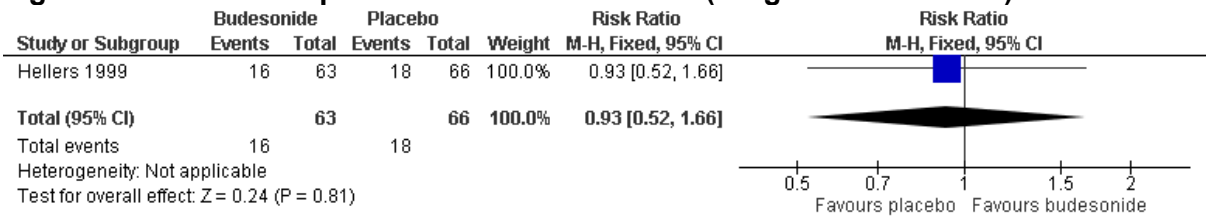
Clinical remission

Figure 24: Clinical remission at 12 months



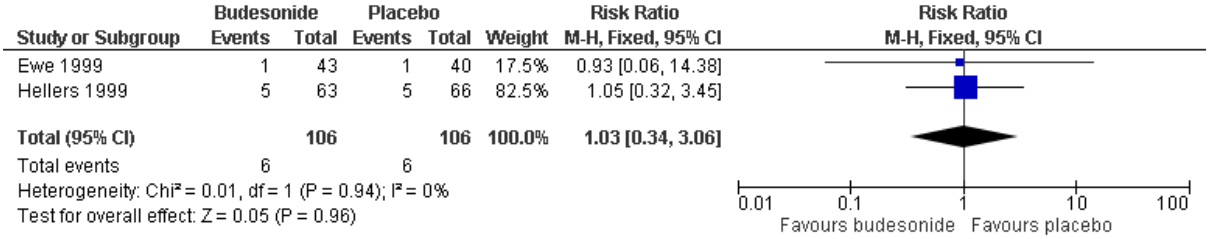
Endoscopic remission

Figure 25: Endoscopic remission at 12 months (Rutgeerts' score < i2)



Withdrawal due to adverse events

Figure 26: Withdrawal due to adverse events at 12 months



Mercaptopurine versus placebo

Clinical remission

Figure 27: Clinical remission at 24 months (clinical assessment)

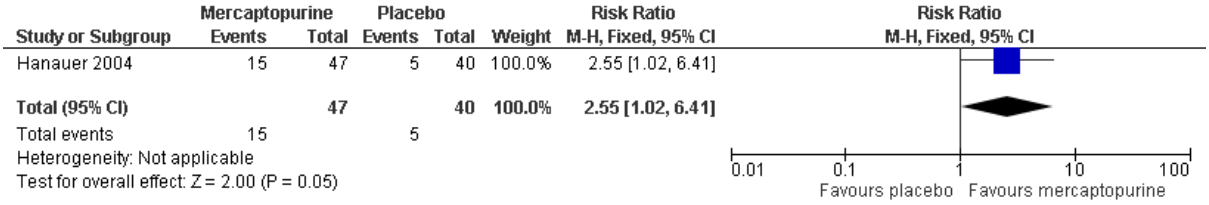
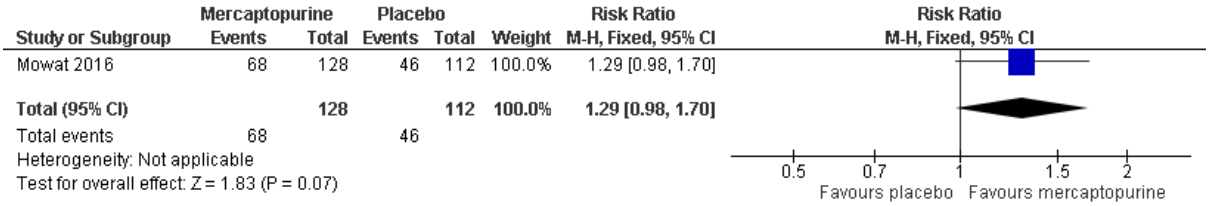


Figure 28: Clinical remission at 36 months ((CDAI < 150, < 100 point increase from baseline and lack of anti-inflammatory rescue treatment)



Endoscopic remission

Figure 29: Endoscopic remission at 24 months (Rutgeerts' score < i2)

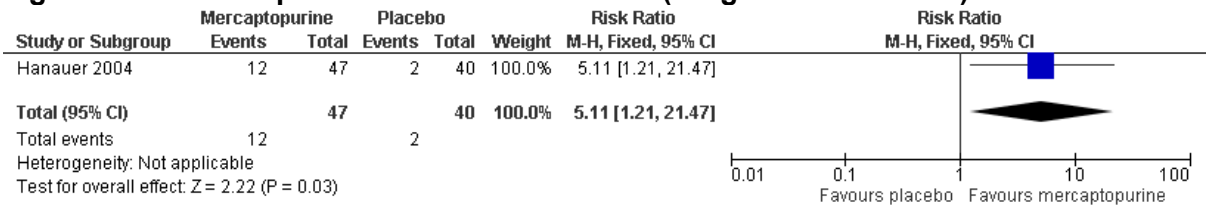
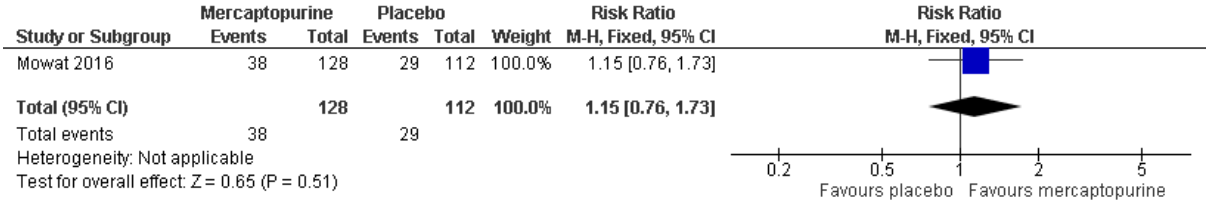


Figure 30: Endoscopic remission at 36 months (Rutgeerts' score < i2)



Withdrawals due to adverse events

Figure 31: Withdrawals due to adverse events at 24 months follow-up

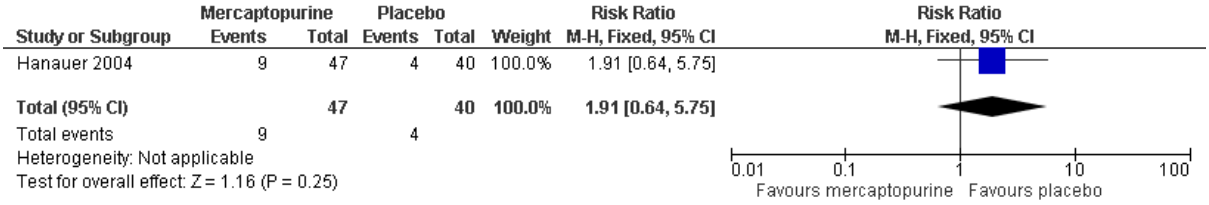
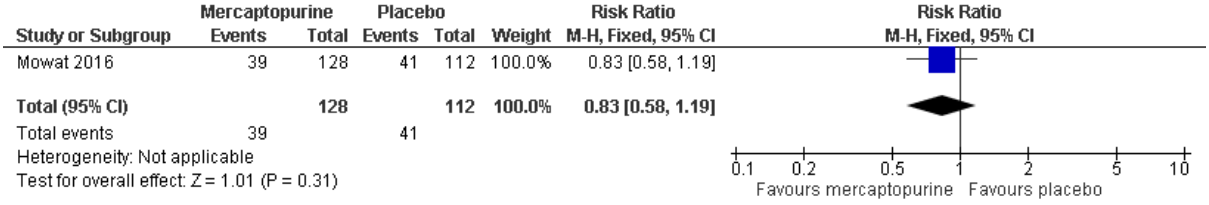
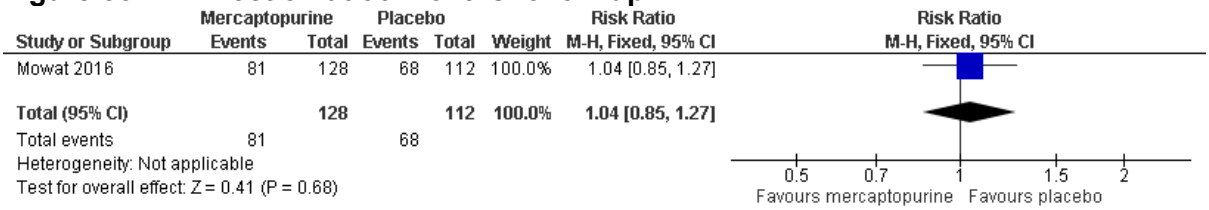


Figure 32: Withdrawals due to adverse events at 36 months follow-up



Adverse events: infection

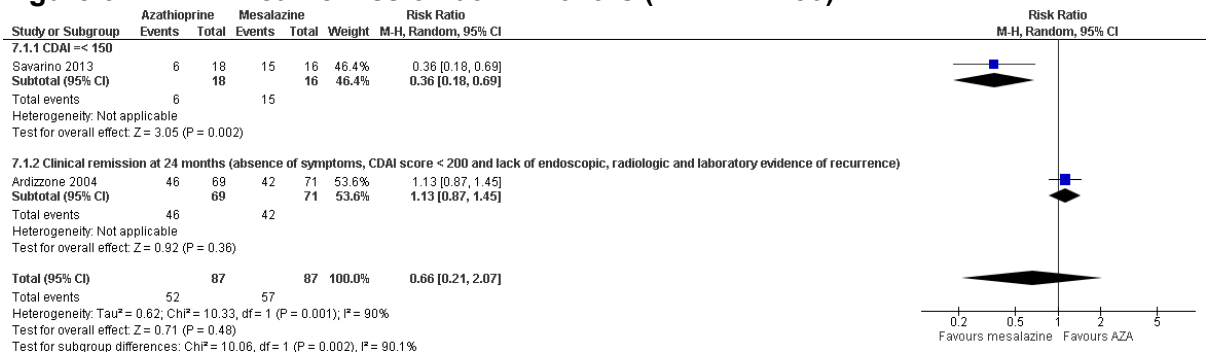
Figure 33: Infection at 36 months follow-up



Azathioprine versus Mesalazine

Clinical remission

Figure 34: Clinical remission at 24 months (CDAI =< 150)



Endoscopic remission

Figure 35: Endoscopic remission at 12 months (Rutgeerts' score < i2)

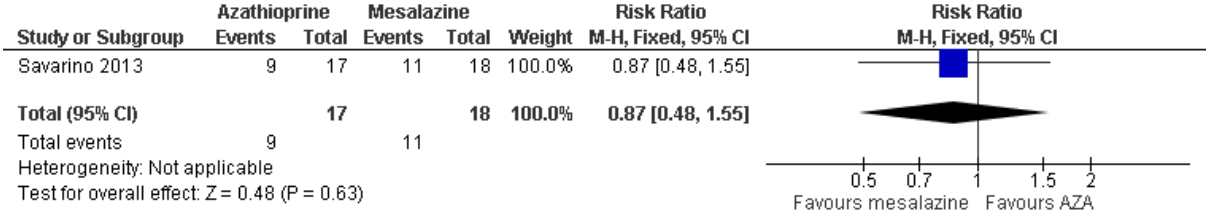
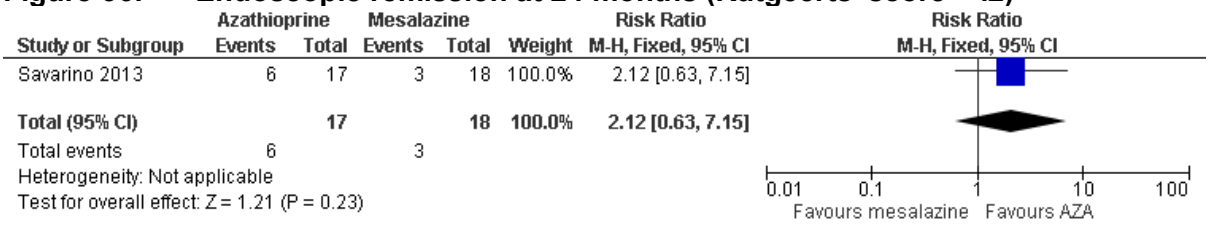
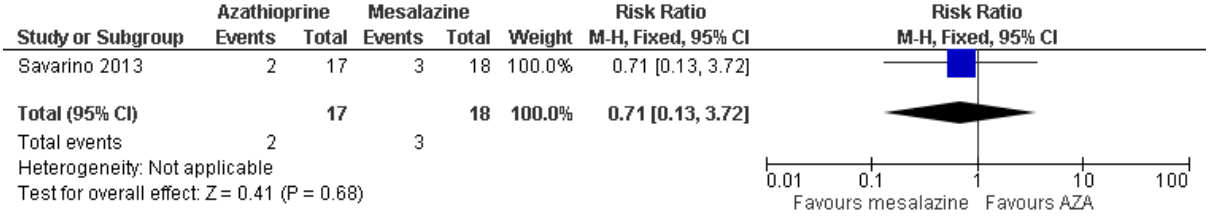


Figure 36: Endoscopic remission at 24 months (Rutgeerts' score < i2)



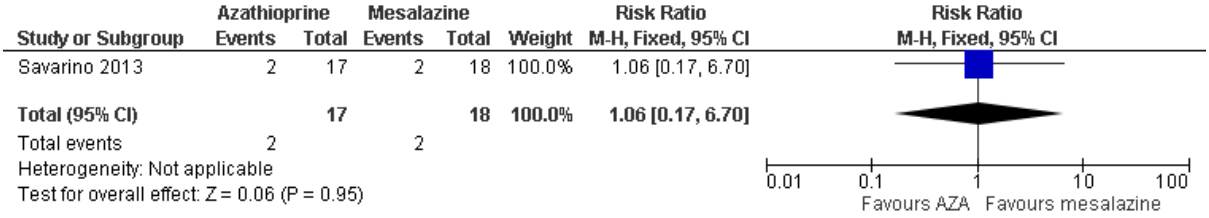
Quality of life

Figure 37: Quality of life at 24 months (IBD-Q > 170) - (score of 170 or more considered to be in remission)



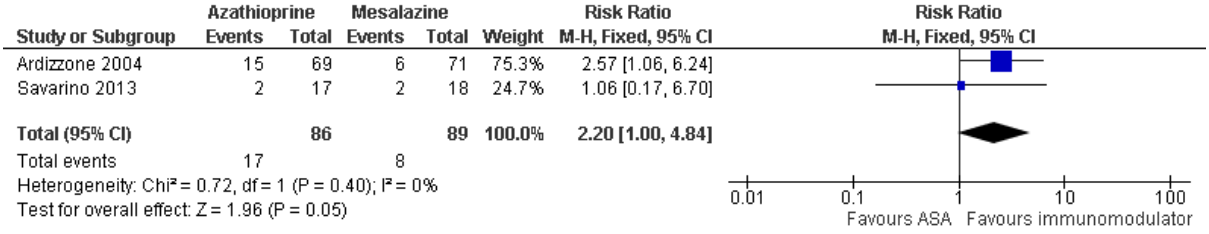
Hospitalisations

Figure 38: Hospitalisations at 24 months



Withdrawal due to adverse events

Figure 39: Withdrawal due to adverse events (24 months follow-up)



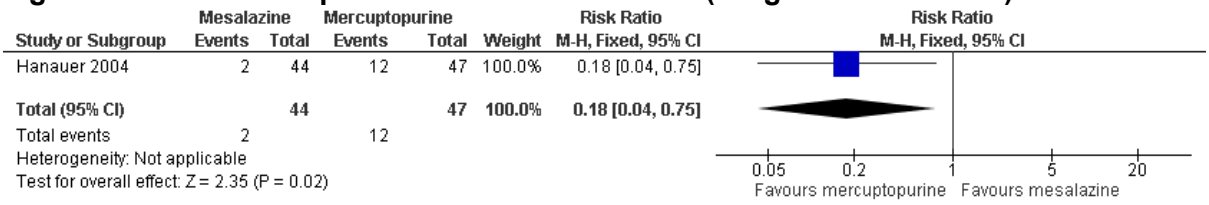
Mesalazine versus mercaptopurine

Clinical remission

Figure 40: Clinical remission at 24 months (clinical assessment)

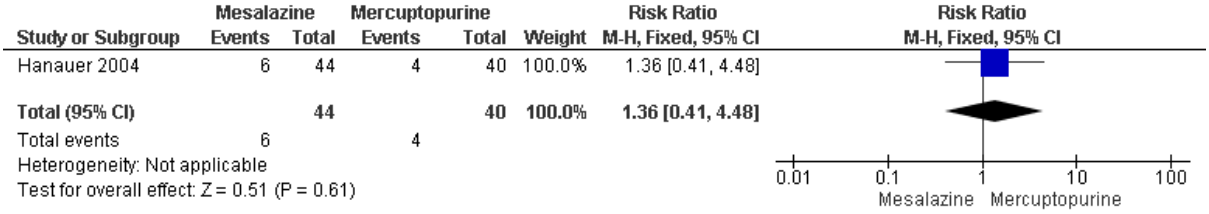
Endoscopic remission

Figure 41: Endoscopic remission at 24 months (Rutgeerts' score < i2)



Withdrawal due to adverse events

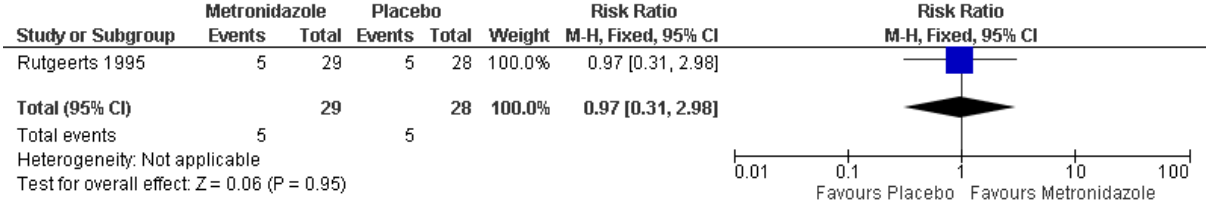
Figure 42: Withdrawal due to adverse events at 24 months



Metronidazole (3 months) versus placebo

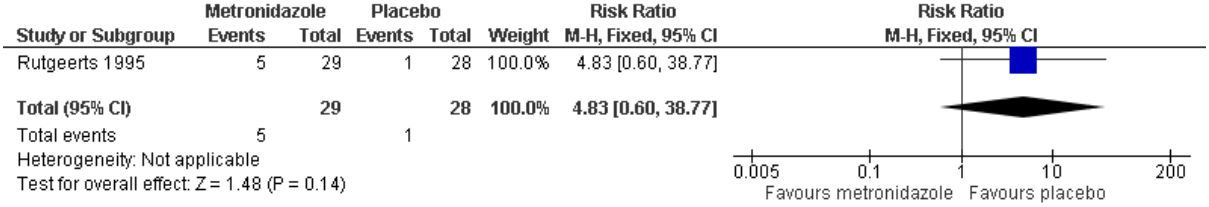
Endoscopic remission

Figure 43: Endoscopic remission at 24 months



Withdrawal due to adverse events

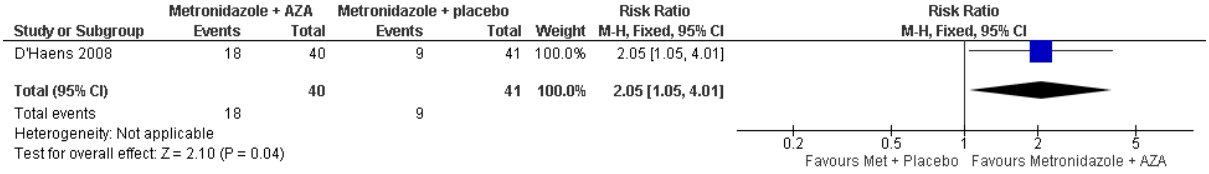
Figure 44: Withdrawal due to adverse events at 36 months (clinical assessment: physician/patient report)



Metronidazole (3 months only) and Azathioprine versus Metronidazole (3 months only) + Placebo

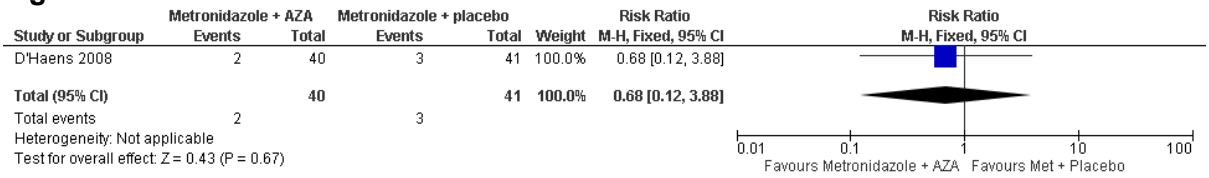
Endoscopic remission

Figure 45: Endoscopic remission at 12 months (Rutgeerts' score < i2)



Withdrawal due to adverse events

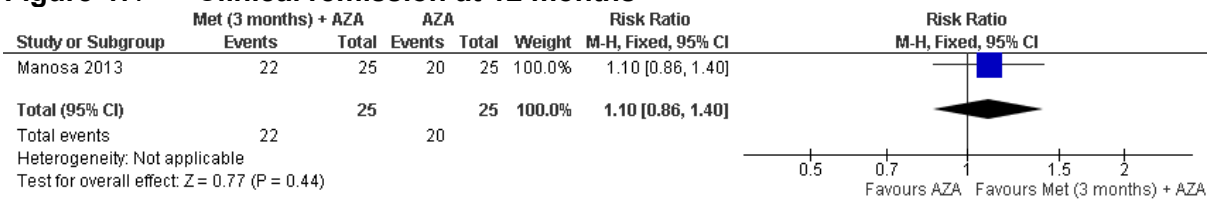
Figure 46: Withdrawal due to adverse events at 12 months



Metronidazole (3 months only) and Azathioprine versus Azathioprine

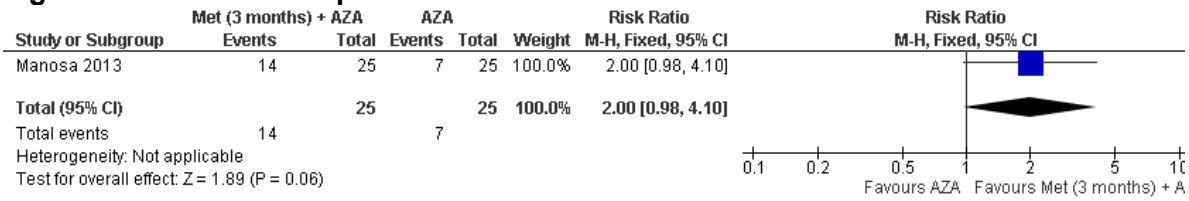
Clinical remission

Figure 47: Clinical remission at 12 months



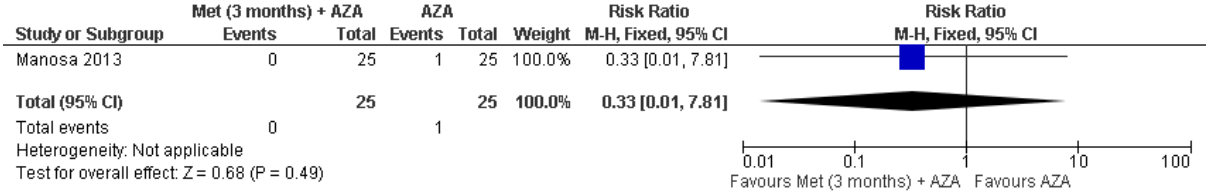
Endoscopic remission

Figure 48: Endoscopic remission at 12 months



Withdrawal due to adverse events

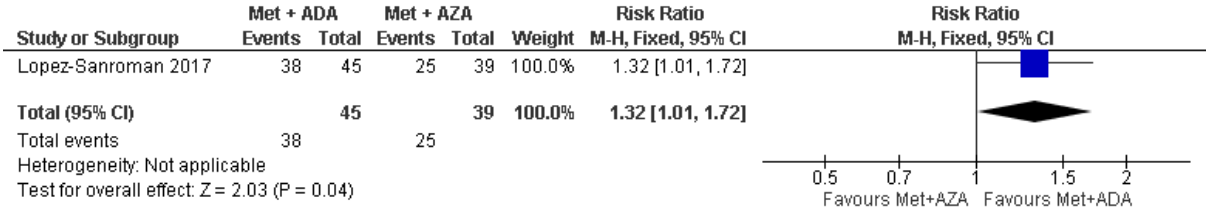
Figure 49: Withdrawal due to adverse events at 12 months



Metronidazole (3 months only) and Adalimumab versus Metronidazole (3 months only) and Azathioprine

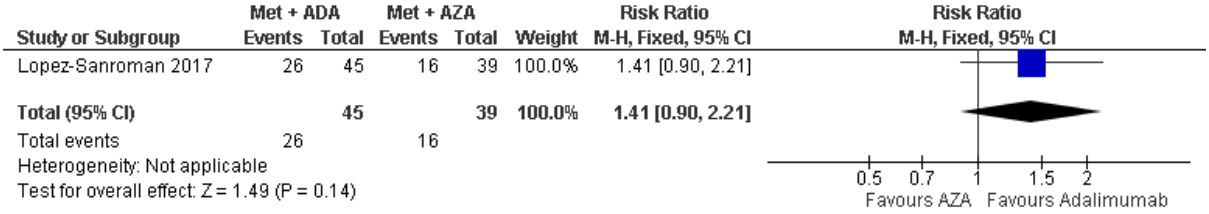
Clinical remission

Figure 50: Clinical remission at 24 months (clinical assessment)



Endoscopic remission

Figure 51: Endoscopic remission at 24 months (Rutgeerts' score < i2)



Withdrawal due to adverse events

Figure 52: Withdrawal due to adverse events at 24 months

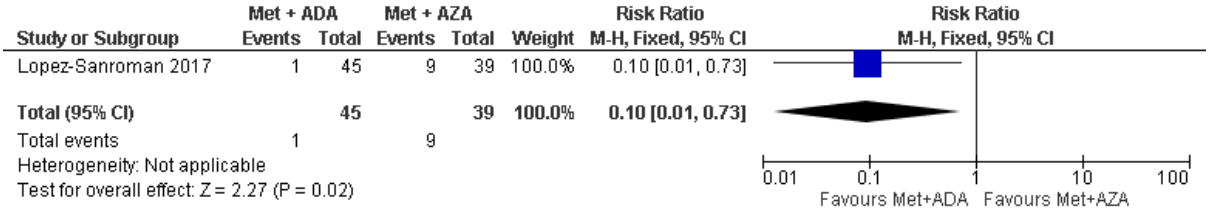
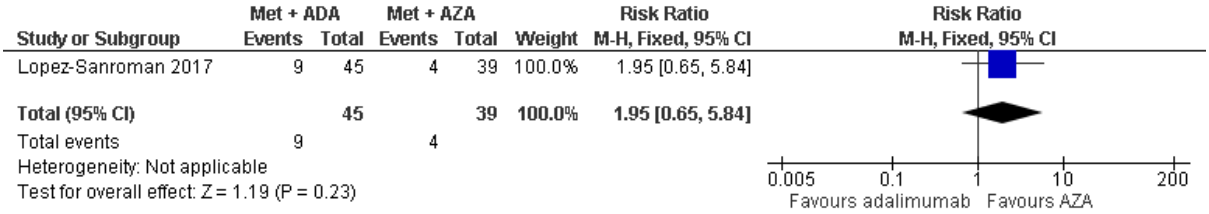


Figure 53: Hospitalisation at 12 months



Infliximab versus placebo

Clinical remission

Figure 54: Clinical remission at 12 months (CDAI < 150)

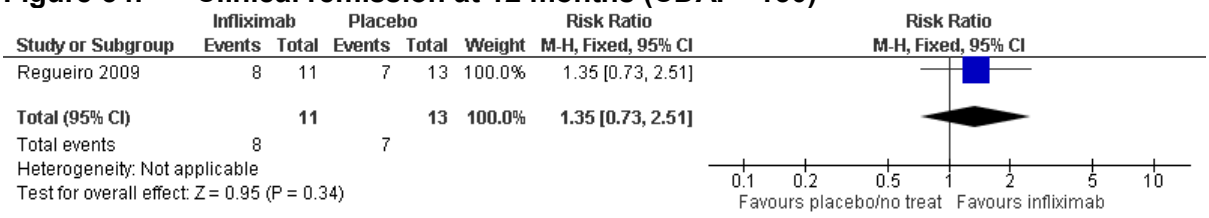
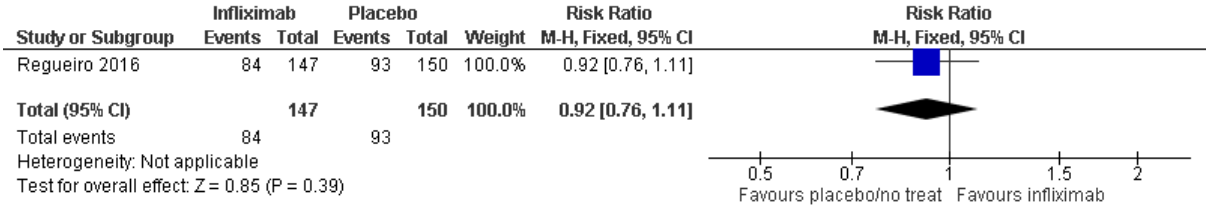


Figure 55: Clinical remission at 17.5 months



Endoscopic remission

Figure 56: Endoscopic remission at 12 months (Rutgeerts' score < i2)

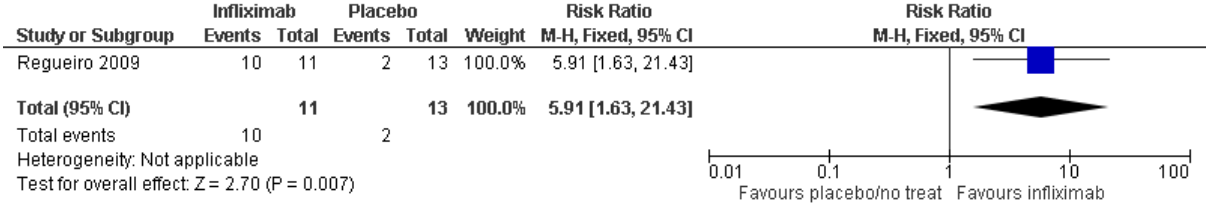
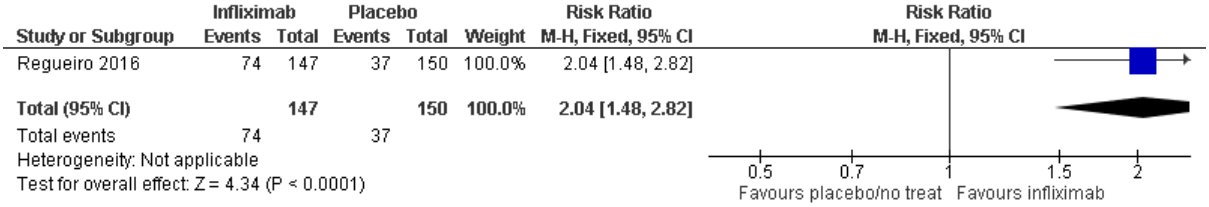
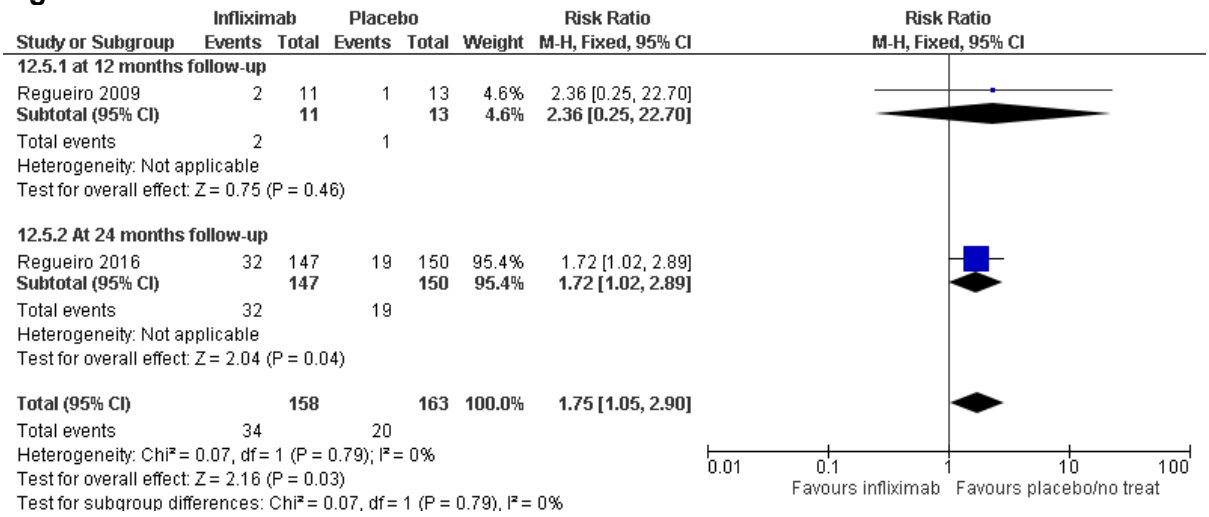


Figure 57: Endoscopic remission at 17.5 months (Rutgeerts' score < i2)



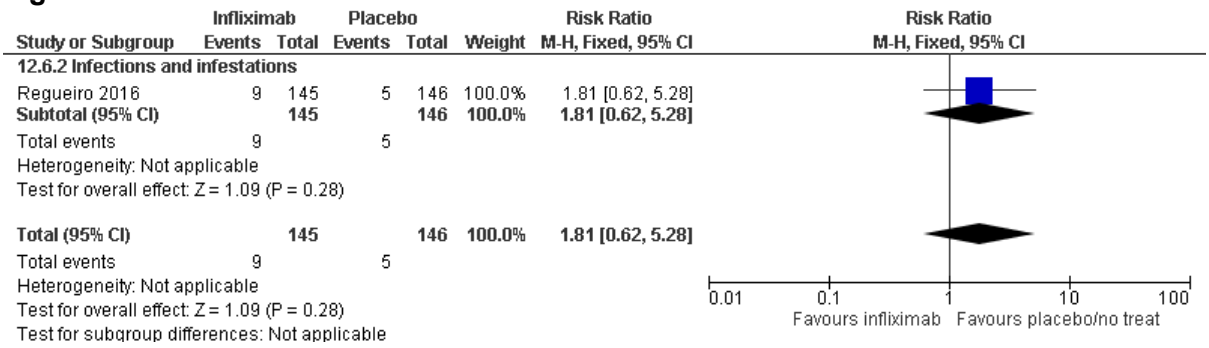
Withdrawal due to adverse events

Figure 58: Withdrawal due to adverse events



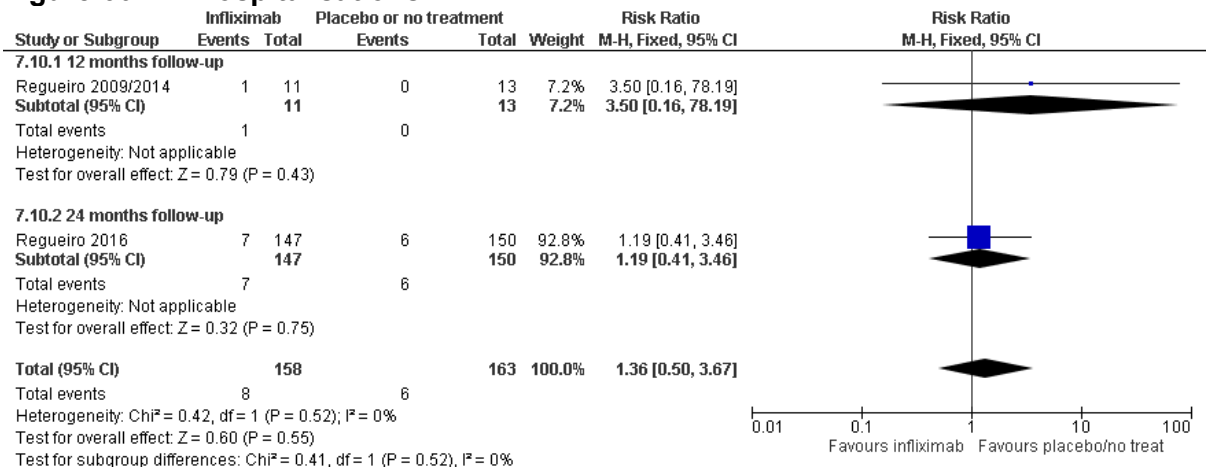
Severe adverse events: infections

Figure 59: Severe adverse events: infections



Hospitalisations

Figure 60: Hospitalisations



Infliximab and mesalazine versus no treatment

Clinical remission

Figure 61: Clinical remission at 12 months (CDAI < 150)

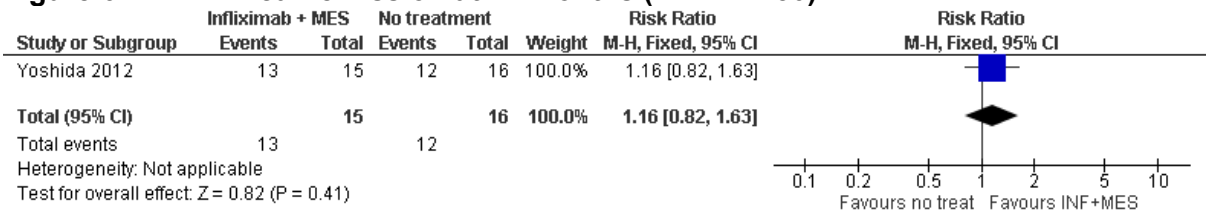
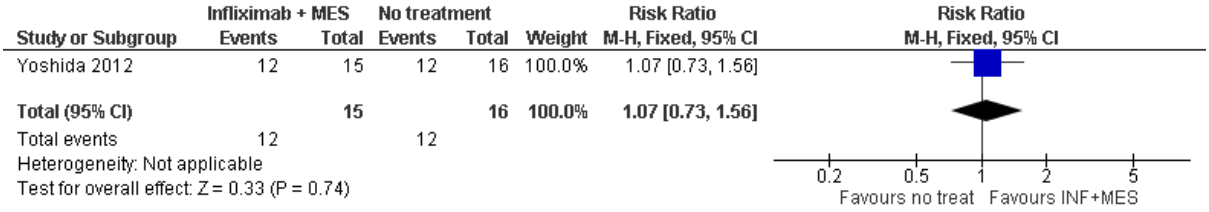
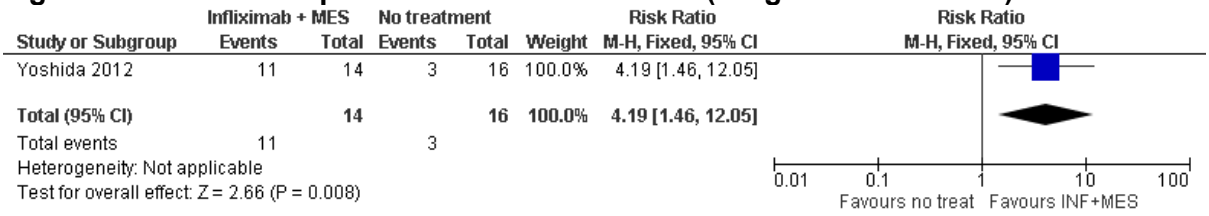


Figure 62: Clinical remission at 36 months (CDAI < 150)



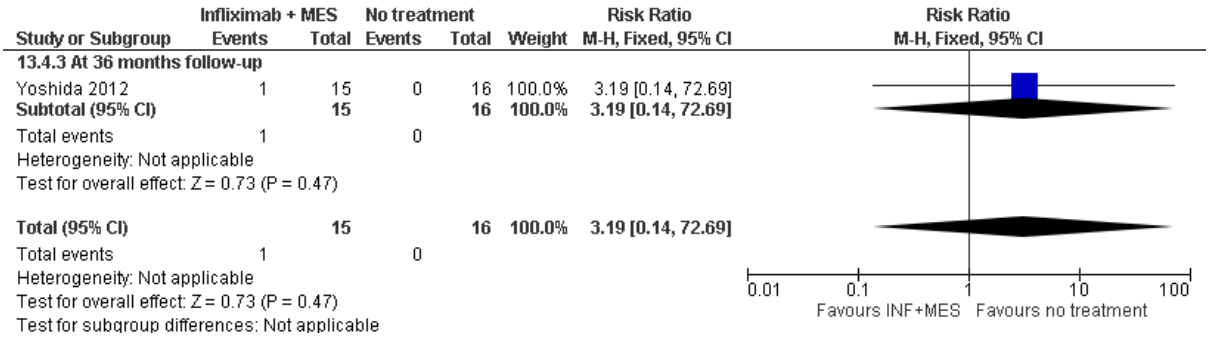
Endoscopic remission

Figure 63: Endoscopic remission at 12 months (Rutgeerts' score < i2)



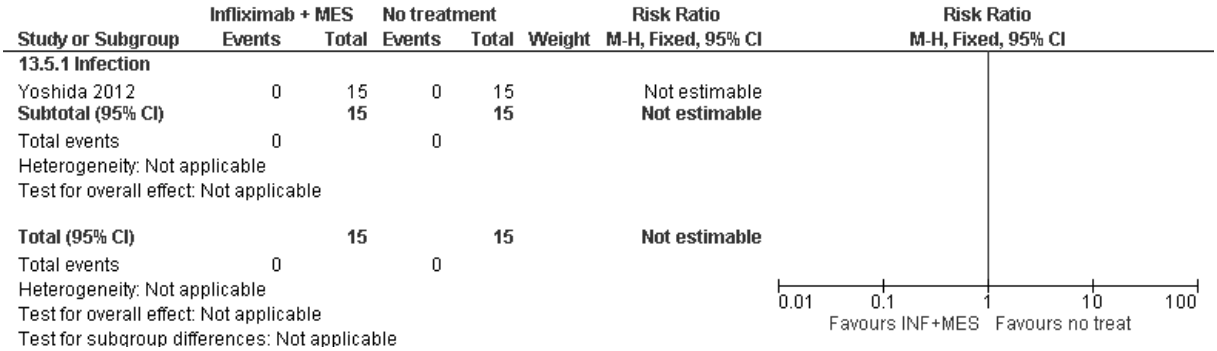
Withdrawal due to adverse events

Figure 64: Withdrawal due to adverse events



Severe adverse events

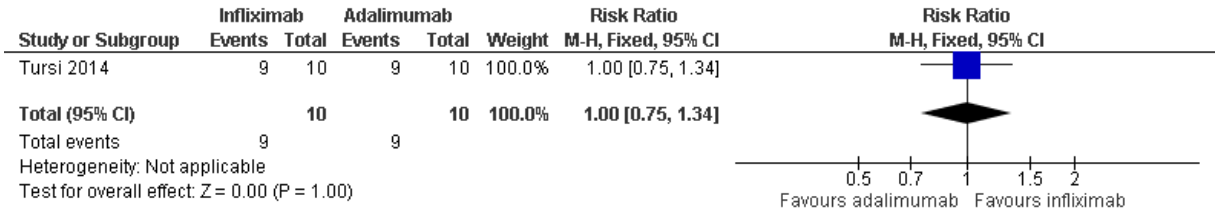
Figure 65: Severe adverse events: infection



Infliximab versus Adalimumab

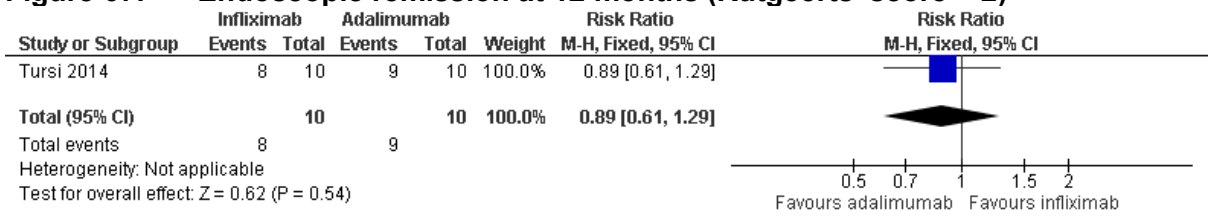
Clinical remission

Figure 66: Clinical remission at 12 months



Endoscopic remission

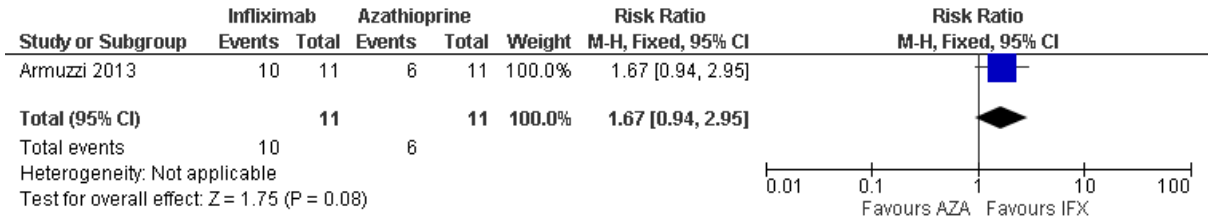
Figure 67: Endoscopic remission at 12 months (Rutgeerts' score < 2)



Infliximab versus Azathioprine

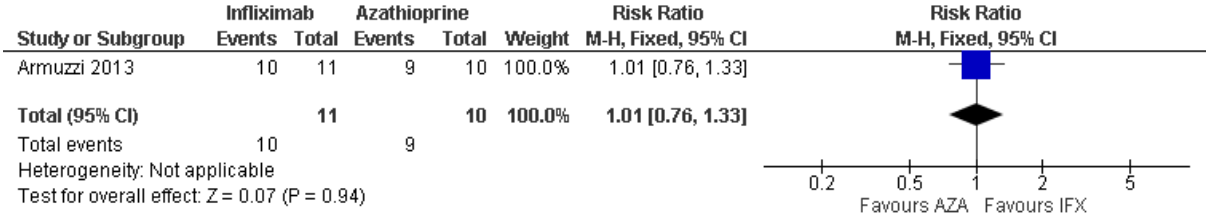
Endoscopic remission

Figure 68: Endoscopic remission at 12 months (Rutgeerts' score < i2)



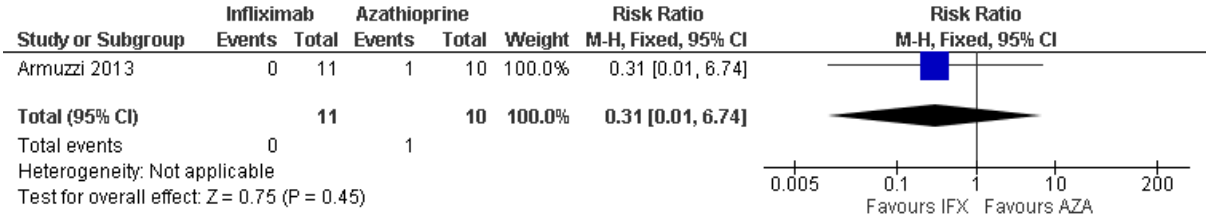
Clinical remission

Figure 69: Clinical remission at 12 months (Harvey-Broadshaw Index (HBI) < 8)



Withdrawal due to adverse events

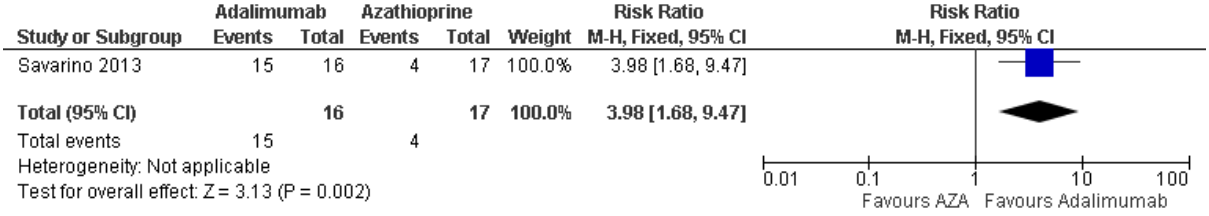
Figure 70: Withdrawal due to adverse events (12 months follow-up)



Adalimumab versus Azathioprine

Clinical remission

Figure 71: Clinical remission at 12 months (CDAI =< 200)



Endoscopic remission

Figure 72: Endoscopic remission at 12 months (Rutgeerts' score < i2)

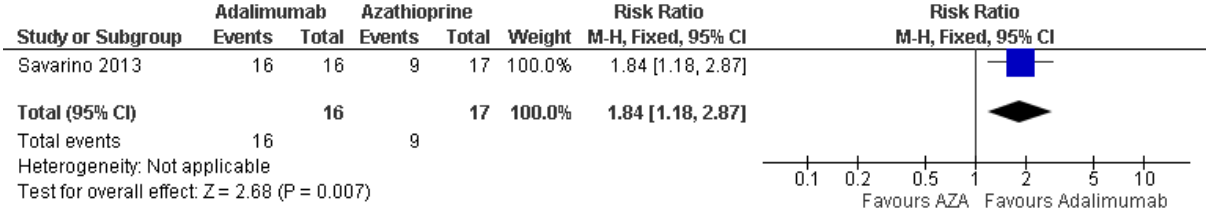
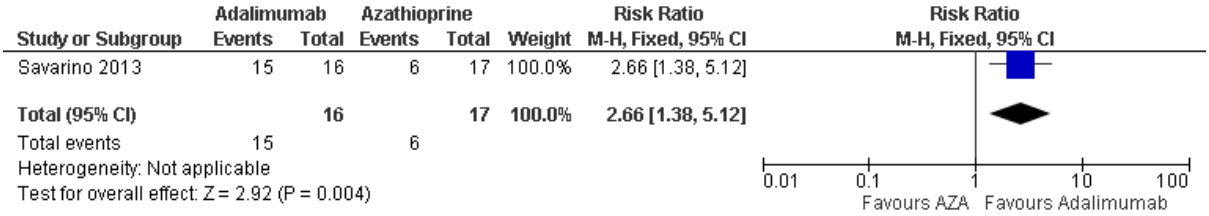
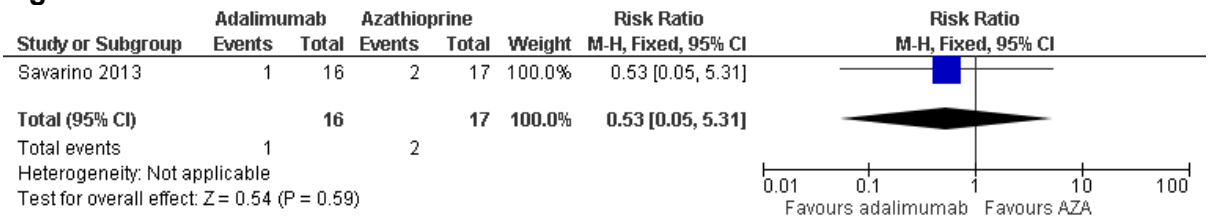


Figure 73: Endoscopic remission at 24 months (Rutgeerts' score < i2)



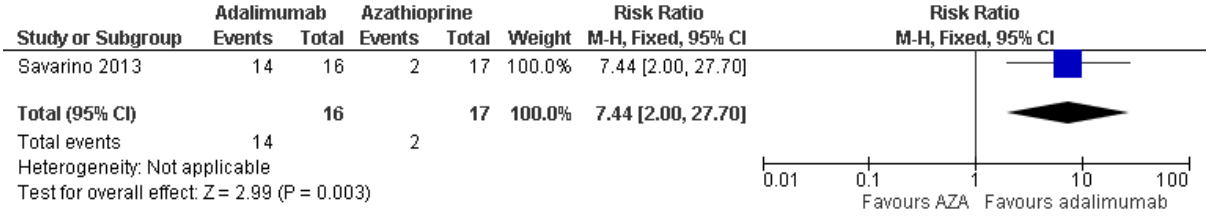
Withdrawal due to adverse events

Figure 74: Withdrawal due to adverse events at 24 months



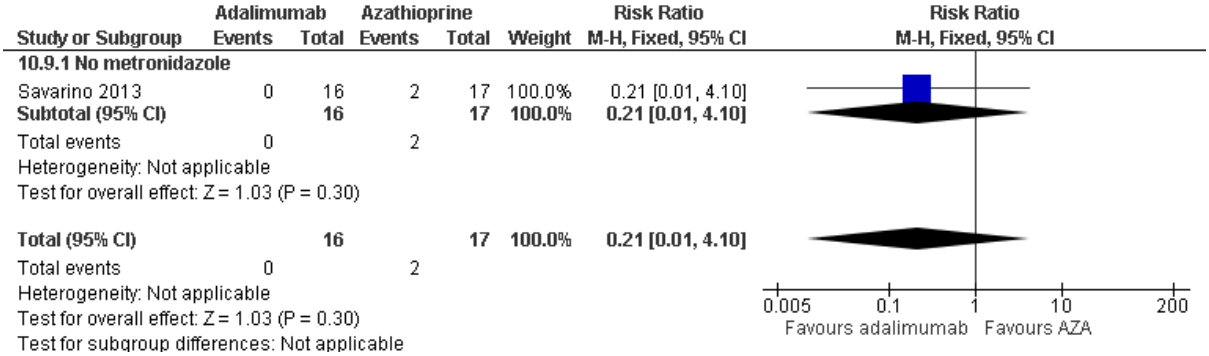
Quality of life

Figure 75: Quality of life at 24 months (IBD-Q > 170) - (score of 170 or more considered to be in remission)



Hospitalisations

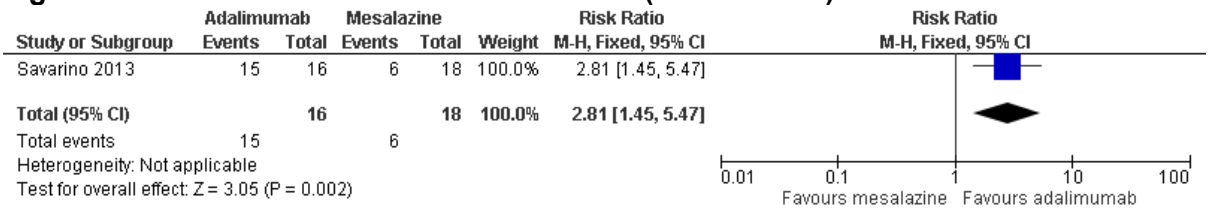
Figure 76: Hospitalisations at 24 months



Adalimumab versus Mesalazine

Clinical remission

Figure 77: Clinical remission at 24 months (CDAI =< 150)



Endoscopic remission

Figure 78: Endoscopic remission at 12 months (Rutgeerts' score < i2)

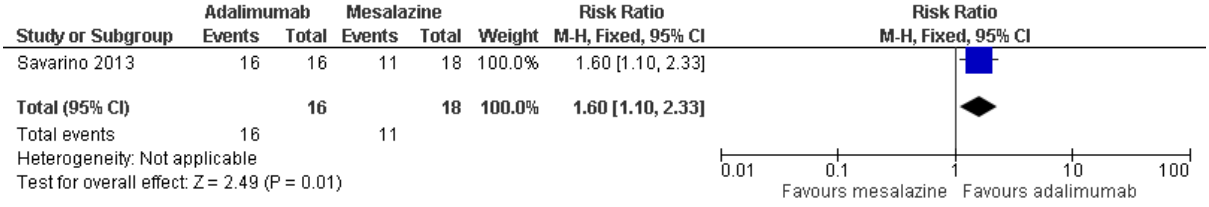
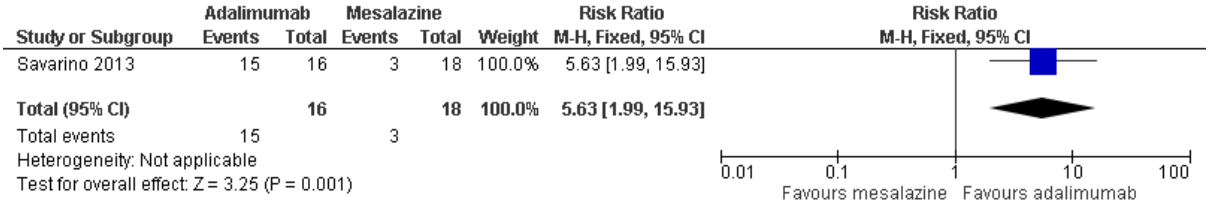
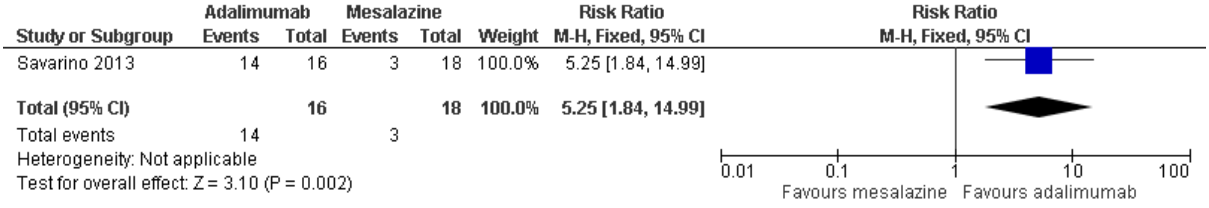


Figure 79: Endoscopic remission at 24 months (Rutgeerts' score < i2)



Quality of life

Figure 80: Quality of life at 24 months (IBD-Q > 170) - (score of 170 or more considered to be in remission)

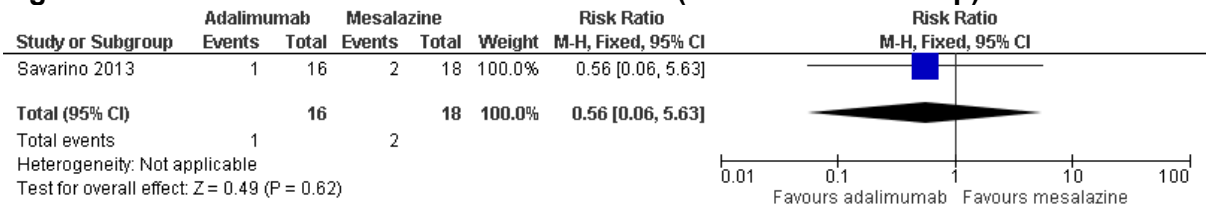


Hospitalisations

Figure 81: Hospitalisations at 24 months

Withdrawal due to adverse events

Figure 82: Withdrawal due to adverse events (24 months follow-up)



Appendix H: GRADE tables

Pairwise analysis

Mesalazine versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: CDAI score < 150 and <100 points from baseline (higher values favour mesalazine)								
1 (Brignola 1995)	RCT	87	RR 1.04 (0.79, 1.39)	No serious	NA[1]	No serious	Very serious[2]	LOW
Clinical remission at 18 months: Absence of: CDAI > 250, CDAI > 200 with 60 point increase, indication for surgery, new fistula or septic complication (higher values favour mesalazine)								
1 (Lochs 2000)	RCT	318	1.05 (0.91, 1.22)	No serious	NA[1]	No serious	No serious	HIGH
Clinical remission at 24 months: Clinical examination (higher values favour mesalazine)								
1 (Hanauer 2004)	RCT	84	RR 1.82 (0.92, 3.57)	Serious[3]	NA[1]	No serious	Serious[4]	LOW
Endoscopic remission at 12 months: Rutgeerts' score = <i2. (Higher values favour mesalazine)								
1 (Brignola 1995)	RCT	87	RR 1.56 (0.96, 2.55)	No serious	NA[1]	No serious	Serious[3]	MODERATE
Endoscopic remission at 18 months: Rutgeerts' score = <2. (Higher values favour mesalazine)								
1 (Lochs 2000)	RCT	318	RR 0.64 (0.39, 1.04)	No serious	NA[1]	No serious	Serious[3]	MODERATE
Endoscopic remission at 24 months: Rutgeerts' score = <i2 (Higher values favour mesalazine)								
1 (Hanauer 2004)	RCT	70	RR 0.68 (0.40, 1.15)	Serious[4]	NA[1]	No serious	Serious[3]	LOW
Withdrawal due to adverse events: 12 months (Lower values favour mesalazine)								
1 (Brignola 1995)	RCT	84	RR 1.52 (0.39, 5.94)	No serious	NA[1]	No serious	Very serious[2]	LOW
Withdrawal due to adverse events: 18 months (Lower values favour mesalazine)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Lochs 2000)	RCT	318	RR 2.55 (1.00, 6.46)	No serious	NA[1]	No serious	Serious[3]	MODERATE
Withdrawal due to adverse events: 24 months (Lower values favour mesalazine)								
1 (Hanauer 2004)	RCT	84	RR 1.36 (0.41, 4.48)	Serious[4]	NA[1]	No serious	Very serious[2]	VERY LOW
Withdrawal due to adverse events: 36 (maximum 72) months (Lower values favour mesalazine)								
1 (McLeod 1995)	RCT	163	RR 2.63 (0.11, 63.50)	No serious	NA[1]	No serious	Very serious[2]	LOW
1 Inconsistency not applicable as effect size is from one study. 2 Very serious imprecision as 95% CI crossed two MIDs. 3 Serious risk of bias due to attrition bias. 4 Serious imprecision as 95% CI crossed one MID.								

Mesalazine versus no treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: CDAI score < 150 (higher values favour mesalazine)								
1 (Caprilli 1994)	RCT	95	1.32 (0.98, 1.79)	Very serious[1]	NA[2]	No serious	Serious[3]	VERY LOW
Clinical remission at 24 months: CDAI score < 150 (higher values favour mesalazine)								
1 (Caprilli 1994)	RCT	95	0.79 (0.48, 1.29)	Very serious[1]	NA[2]	No serious	Very serious[4]	VERY LOW
Endoscopic remission at 12 months: Rutgeerts' score = i0. (Higher values favour mesalazine)								
1 (Caprilli 1994)	RCT	95	1.77 (1.08, 2.90)	Serious[5]	NA[2]	No serious	Serious[3]	LOW
Endoscopic remission at 24 months: Rutgeerts' score = i0. (Higher values favour mesalazine)								
1 (Caprilli 1994)	RCT	95	2.04 (0.54, 7.69)	Serious[5]	NA[2]	No serious	Very serious[4]	VERY LOW
Withdrawal due to adverse events: 12 months (Lower values favour mesalazine)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Caprilli 1994)	RCT	95	5.10 (0.25, 103.57)	Serious[5]	NA[2]	No serious	Very serious[4]	VERY LOW
Withdrawal due to adverse events: 12 months (Lower values favour mesalazine)								
1 (Caprilli 1994)	RCT	95	5.10 (0.25, 103.57)	Serious[5]	NA[2]	No serious	Very serious[4]	VERY LOW

1 Very serious risk of bias due to participation and detection bias in subjective outcome (no blinding).
2 Inconsistency not applicable as effect size is from one study.
3 Serious imprecision as 95% CI crossed one MID.
4 Very serious imprecision as 95% CI crossed two MIDs.
5 Serious risk of bias due to participation and detection bias (no blinding).

Sulfasalazine versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: Clinical examination, CDAI score (not described) and blood tests. (higher values favour ASA)								
1 (Ewe 1989)	RCT	232	RR 1.17 (1.01, 1.34)	No serious	NA[1]	No serious	Serious[2]	MODERATE
Clinical remission at 24 months: Clinical examination, CDAI score (not described) and blood tests. (higher values favour ASA)								
1 (Ewe 1989)	RCT	232	RR 1.22 (1.02, 1.45)	No serious	NA[1]	No serious	Serious[2]	MODERATE
Clinical remission at 36 (maximum 72) months: Clinical examination, CDAI score (not described) and blood tests. (higher values favour ASA)								
1 (Ewe 1989)	RCT	232	1.09 (0.64, 1.86)	No serious	NA[1]	No serious	Very serious[3]	LOW

1 Inconsistency not applicable as effect size is from one study.
2 Serious imprecision as 95% CI crossed one MID.
3 Very serious imprecision as 95% CI crossed two MIDs.

Budesonide versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: CDAI <150 (higher values favour budesonide)								
1 (Ewe 1999)	RCT	83	RR 1.28 (0.90, 1.84)	Serious[1]	NA[2]	No serious	Serious[3]	LOW
Endoscopic remission at 12 months: Rutgeerts' score < i2 (higher values favour budesonide)								
1 (Ewe 1999)	RCT	129	RR 1.08 (0.78, 1.49)	Serious[1]	NA[2]	No serious	Very serious[4]	VERY LOW
Withdrawal due to adverse events at 12 months (Lower values favour budesonide)								
2 (Ewe 1999; Hellers 1999)	RCT	212	RR 1.03 (0.34. 3.06)	Serious[1]	No serious	No serious	Very serious[4]	VERY LOW
1 Moderate risk of bias due to attrition bias. 2 Inconsistency not applicable as effect size is from one study. 3 Serious imprecision as 95% CI crossed one MID. 4 Very serious imprecision as 95% CI crossed two MIDs.								

Mercaptopurine versis placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 24 months: clinical assessment (higher values favour Mercuptopruine)								
1 (Hanauer 2004)	RCT	87	RR 2.55 (1.02, 6.41)	Serious[1]	NA[2]	No serious	Serious[3]	LOW
Clinical remission at 36 months: CDAI <150, <100 point increase from baseline and lack of anti-inflammatory rescue treatment (higher values favour mercuptopurine)								
1 (Mowat 2016)	RCT	240	RR 1.29 (0.98, 1.70)	No serious	NA[2]	No serious	Serious[3]	MODERATE
Endoscopic remission at 24 months: Rutgeerts' score < i2 (higher values favour mercuptopurine)								
1 (Hanauer 2004)	RCT	87	RR 5.11 (1.21, 21.47)	Serious[1]	NA[2]	No serious	Serious[3]	LOW
Endoscopic remission at 36 months: Rutgeerts' score < i2 (higher values favour mercuptopurine)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Mowat 2016)	RCT	240	RR 1.15 (0.76, 1.73)	No serious	NA[2]	No serious	Very serious[4]	LOW
Withdrawal due to adverse events at 24 months (Lower values immunomodulator: Mercuptopurine)								
1 (Hanauer 2004)	RCT	87	RR 1.91 (0.64, 5.75)	Serious[1]	NA[2]	No serious	Very serious[4]	VERY LOW
Withdrawal due to adverse events at 36 months (Lower values immunomodulator: Mercuptopurine 1 mg/kg rounded to nearest 25mg)								
1 (Mowat 2016)	RCT	240	RR 0.83 (0.58, 1.19)	Serious[1]	NA[2]	No serious	Serious[4]	LOW
Adverse events: infection, 36 months follow-up (Lower values favour mercuptopurine)								
1 (Mowat 2016)	RCT	140	RR 1.04 (0.85, 1.27)	No serious	NA[2]	No serious	Serious[3]	MODERATE
1 Moderate risk of bias due to attrition bias. 2 Inconsistency not applicable as effect size is from one study. 3 Serious imprecision as 95% CI crossed one MID. 4 Very serious imprecision as 95% CI crossed two MIDs.								

Azathioprine versus mesalazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 24 months (higher values favour AZA)								
2 (Savarino 2013; Ardizzone 2004)	RCT	174	RR 0.66 (0.21, 2.07)	Very serious[1]	Very serious[2]	No serious	Very serious[3]	VERY LOW
Endoscopic remission at 12 months: Rutgeers' score <2 (higher values favour AZA)								
1 (Savarino 2013)	RCT	35	RR 0.87 (0.48, 1.55)	Serious[4]	NA[5]	No serious	Very serious[3]	VERY LOW
Endoscopic remission at 24 months: Rutgeers' score <2 (higher values favour AZA)								
1 (Savarino 2013)	RCT	35	RR 2.12 (0.63, 7.15)	Serious[4]	NA[5]	No serious	Very serious[3]	VERY LOW

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Withdrawal due to adverse events at 24 months (Lower values favour AZA)								
2 (Savarino 2013; Ardizzone 2004)	RCT	175	RR 2.20 (1.00, 4.84)	Serious[4]	NA[5]	No serious	Serious[6]	LOW
Hospitalisation (Lower values favour AZA)								
1 (Savarino 2013)	RCT	35	RR 1.06 (0.17, 6.70)	Serious[4]	NA[5]	No serious	Very serious[3]	VERY LOW
Quality of life at 24 months: IBD-Q>170 (considered to be in remission) (Higher values favour AZA)								
1 (Savarino 2013)	RCT	35	RR 0.71 (0.13, 3.72)	Very serious[1]	NA[5]	No serious	Very serious[3]	VERY LOW
1 High risk of bias due to participation and detection bias in subjective outcome (no blinding). 2 I^2 greater than 66.7%. 3 Very serious imprecision as 95% CI crossed two MIDs. 4 Moderate risk of bias due to participation and detection bias (no blinding). 5 Inconsistency not applicable as effect size is from one study. 6 Moderate imprecision as 95% CI crossed one MID.								

Mesalazine versus mercaptopurine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 24 months: Clinical examination (higher values favour mesalazine)								
1 (Hanauer 2004)	RCT	91	RR 0.78 (0.40, 1.52)	Serious[1]	NA[2]	No serious	Very serious[2]	VERY LOW
Endoscopic remission at 24 months: Rutgeerts' score <i2. (higher values favour mesalazine)								
1 (Hanauer 2004)	RCT	91	RR 0.18 (0.04, 0.75)	Serious[1]	NA[2]	No serious	No serious	MODERATE
Withdrawal due to adverse events at 24 months (lower values favour mesalazine)								
1 (Hanauer 2004)	RCT	84	RR 1.36 (0.41, 4.48)	Serious[1]	NA[2]	No serious	Very serious[2]	VERY LOW

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Moderate risk of bias due to attrition bias. 2 Inconsistency not applicable as effect size is from one study. 3 Very serious imprecision as 95% CI crossed two MIDs.								

Metronidazole (3 months) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Endoscopic remission at 36 months: Rutgeerts' score i0 (higher values favour metronidazole)								
1 (Rutgeerts 1995)	RCT	57	RR 0.97 (0.31, 2.98)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
Withdrawal due to adverse events at 36 months: Physician/patient report (lower values favour metronidazole)								
1 (Rutgeerts 1995)	RCT	57	RR 4.83 (0.60, 38.77)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
1 Moderate risk of bias due to attrition bias. 2 Inconsistency not applicable as effect size is from one study. 3 Very serious imprecision as 95% CI crossed two MIDs.								

Metronidazole (3 months) and azathioprine versus metronidazole (3 months) and placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Endoscopic remission at 12 months: Rutgeerts' score < i2 (higher values favour metronidazole and azathioprine)								
1 (D'Haens 2008)	RCT	81	RR 2.05 (1.05, 4.01)	Serious[1]	NA[2]	No serious	Serious[3]	LOW
Withdrawal due to adverse events at 36 months: Physician/patient report (lower values favour metronidazole and azathioprine)								
1 (D'Haens 2008)	RCT	81	RR 0.68 (0.12, 3.88)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
1 Moderate risk of bias due to attrition bias. 2 Inconsistency not applicable as effect size is from one study. 3 Serious imprecision as 95% CI crossed one MID. 4 Very serious imprecision as 95% CI crossed two MIDs.								

Metronidazole (3 months) and azathioprine versus azathioprine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months (higher values favour AZA plus metronidazole)								
1 (Manosa 2013)	RCT	50	RR 1.10 (0.86, 1.40)	No serious	NA[1]	No serious	Serious[2]	MODERATE
Endoscopic remission at 12 months: Rutgeerts' score < i2 (higher values favour AZA plus metronidazole)								
1 (Manosa 2013)	RCT	50	RR 2.00 (0.98, 4.10)	No serious	NA[1]	No serious	Serious[2]	MODERATE
Withdrawal due to adverse events at 12 months (Lower values favour AZA plus metronidazole)								
1 (Manosa 2013)	RCT	50	RR 0.33 (0.01, 7.81)	No serious	NA[1]	No serious	Very serious[3]	LOW

1. Inconsistency not applicable as effect size is from one study.
2. Serious imprecision as 95% CI crossed one MID.
3. Very serious imprecision as 95% CI crossed two MIDs.

Metronidazole (3 months) and adalimumab versus metronidazole (3 months) and azathioprine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: CDAI=<200 (higher values favour adalimumab)								
1 (Lopez-Sanroman 2017)	RCT	84	RR 1.32 (1.01, 1.72)	Very serious[1]	NA[2]	No serious	Serious[3]	VERY LOW
Endoscopic remission at 12 months: Rutgeerts' score < i2 (higher values favour metronidazole and adalimumab)								
1 (Lopez-Sanroman 2017)	RCT	84	RR 1.41 (0.90, 2.21)	Serious[4]	NA[2]	No serious	Serious[3]	LOW
Withdrawal due to adverse events at 12 months (lower values favour metronidazole and adalimumab)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Lopez-Sanroman 2017)	RCT	84	RR 0.10 (0.01, 0.73)	Serious[4]	NA[2]	No serious	No serious	MODERATE
Hospitalisation: 3-months metronidazole treatment (lower values favour metronidazole and adalimumab)								
1 (Lopez-Sanroman 2017)	RCT	84	RR 1.95 (0.65, 5.84)	Very serious[1]	NA[2]	No serious	Very serious[5]	VERY LOW
1 High risk of bias due to participation and detection bias in subjective outcome (no blinding). 2 Inconsistency not applicable as effect size is from one study. 3 Serious imprecision as 95% CI crossed one MID. 4 Moderate risk of bias due to participation and detection bias (no blinding). 5 Very serious imprecision as 95% CI crossed two MIDs.								

Infliximab versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: CDAI <150 (higher values favour infliximab)								
1 (Regueiro 2009)	RCT	24	RR 1.35 (0.73, 2.51)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
Endoscopic remission at 12 months: Rutgeerts' score <i2 (higher values favour infliximab)								
1 (Regueiro 2009)	RCT	24	RR 5.91 (1.63, 21.43)	Serious[1]	NA[2]	No serious	No serious	MODERATE
Endoscopic remission at 17.5 months: Rutgeerts' score <i2 (higher values favour infliximab)								
1 (Regueiro 2016)	RCT	297	RR 1.59 (1.32, 1.92)	Serious[1]	NA[2]	No serious	No serious	MODERATE
Clinical remission at 17.5 months: CDAI =< 200 and Rutgeerts' score < i2 (higher values favour infliximab)								
1 (Regueiro 2016)	RCT	297	RR 0.92 (0.76, 1.11)	Serious[1]	NA[2]	No serious	Serious[4]	LOW
Withdrawal due to adverse events: At 12 months follow-up (lower values favour infliximab)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Regueiro 2009)	RCT	24	RR 2.36 (0.25, 22.70)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
Withdrawal due to adverse events: At 24 months follow-up (lower values favour infliximab)								
1 (Regueiro 2016)	RCT	297	RR 1.72 (1.02, 2.89)	Serious[1]	NA	No serious	Serious[4]	LOW
Severe adverse event: Infection and infestations (lower values favour infliximab)								
1 (Regueiro 2016)	RCT	291	RR 1.81 (0.62, 5.28)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
Hospitalisation: 12 months follow-up (Lower values favour infliximab)								
1 (Regueiro 2009)	RCT	24	RR 3.50 (0.16, 78.19)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
Hospitalisation: 24 months follow-up (Lower values favour infliximab)								
1(Regueiro 2016)	RCT	297	RR 1.19 (0.41, 3.46)	Serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
1 Moderate risk of bias. 2 Inconsistency not applicable as effect size is from one study. 3 Very serious imprecision as 95% CI crossed two MIDs. 4 Serious imprecision as 95% CI crossed one MID.								

Infliximab and mesalazine versus no treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: CDAI <150 (higher values favour infliximab and mesalazine)								
1 (Yoshida 2012)	RCT	31	RR 1.16 (0.82, 1.63)	Very serious[1]	NA[2]	No serious	Serious[3]	VERY LOW
Clinical remission at 12 months: CDAI <150 (higher values favour infliximab and mesalazine)								
1 (Yoshida 2012)	RCT	31	RR 1.07 (0.73, 1.56)	Very serious[1]	NA[2]	No serious	Very serious[4]	VERY LOW
Endoscopic remission at 12 months: Rutgeerts' score <i2 (higher values favour infliximab and mesalazine)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Yoshida 2012)	RCT	30	RR 4.19 (1.46, 12.05)	Serious[5]	NA[2]	No serious	No serious	MODERATE
Withdrawal due to adverse events: At 36 months follow-up (Lower values favour infliximab)								
1 (Yoshida 2012)	RCT	31	RR 3.19 (0.14, 72.69	Serious[5]	NA[2]	No serious	Very serious[5]	VERY LOW
Severe adverse event: Infection (Lower values favour infliximab)								
1 (Yoshida 2012)	RCT	30	Not estimable	Serious[5]	NA	No serious	NA	MODERATE
1 High risk of bias due to participation and detection bias in subjective outcome (no blinding). 2 Inconsistency not applicable as effect size is from one study. 3 Serious imprecision as 95% CI crossed one MID. 4 Very serious imprecision as 95% CI crossed two MIDs. 5 Moderate risk of bias due to participation and detection bias (no blinding).								

Adalimumab versus azathioprine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 24 months: CDAI=<150 (higher values favour adalimumab)								
1 (Savarino 2013)	RCT	33	RR 3.98 (1.68, 9.47)	Very serious[1]	NA[2]	No serious	No serious	LOW
Endoscopic remission at 12 months: Rutgeers' score <i2 (higher values favour adalimumab)								
1 (Savarino 2013)	RCT	33	RR 1.84 (1.18, 2.87)	Serious[3]	NA[2]	No serious	Serious[4]	LOW
Endoscopic remission at 24 months: Rutgeers' score <i2 (higher values favour adalimumab)								
1 (Savarino 2013)	RCT	33	RR 2.66 (1.38, 5.12)	Serious[3]	NA[2]	No serious	No serious	MODERATE
Withdrawal due to adverse events (lower values favour adalimumab)								
1 (Savarino 2013)	RCT	33	RR 0.53 (0.05, 5.31)	Serious[3]	NA[2]	No serious	Very serious[5]	VERY LOW
Hospitalisation (lower values favour adalimumab)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Savarino 2013)	RCT	33	RR 0.21 (0.01, 4.10)	Serious[3]	NA[2]	No serious	Very serious[2]	VERY LOW
Quality of life at 24 months: IBD-Q>170 (considered to be in remission) (Higher values favour adalimumab)								
1 (Savarino 2013)	RCT	33	RR 7.44 (2.00, 27.70)	Very serious[1]	NA[2]	No serious	No serious	LOW

1 High risk of bias due to participation and detection bias in subjective outcome (no blinding).
2 Inconsistency not applicable as effect size is from one study.
3 Moderate risk of bias due to participation and detection bias (no blinding).
4 Serious imprecision as 95% CI crossed one MID.
5 Very serious imprecision as 95% CI crossed two MIDs.

Adalimimab versus mesalazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 24 months: CDAI=<150 (higher values favour adalimumab)								
1 (Savarino 2013)	RCT	34	RR 2.81 (1.45, 5.47)	Very serious[1]	NA[2]	No serious	No serious	LOW
Endoscopic remission at 12 months: Rutgeers' score <i2 (higher values favour adalimumab)								
1 (Savarino 2013)	RCT	34	RR 1.60 (1.10, 2.33)	Serious[3]	NA[2]	No serious	Serious[4]	LOW
Endoscopic remission at 24 months: Rutgeers' score <i2 (higher values favour adalimumab)								
1 (Savarino 2013)	RCT	34	RR 5.63 (1.99, 15.93)	Serious[3]	NA[2]	No serious	No serious	MODERATE
Withdrawal due to adverse events (lower values favour adalimumab)								
1 (Savarino 2013)	RCT	34	RR 0.56 (0.06, 5.63)	Serious[3]	NA[2]	No serious	Very serious[5]	VERY LOW
Hospitalisation (lower values favour adalimumab)								
1 (Savarino 2013)	RCT	34	RR 0.22 (0.01, 4.34)	Serious[3]	NA[2]	No serious	Very serious[2]	VERY LOW
Quality of life at 24 months: IBD-Q>170 (considered to be in remission) (Higher values favour adalimumab)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Savarino 2013)	RCT	34	RR 5.25 [1.84, 14.99]	Very serious[1]	NA[2]	No serious	No serious	LOW

1 High risk of bias due to participation and detection bias in subjective outcome (no blinding).
2 Inconsistency not applicable as effect size is from one study.
3 Moderate risk of bias due to participation and detection bias (no blinding).
4 Serious imprecision as 95% CI crossed one MID.
5 Very serious imprecision as 95% CI crossed two MIDs.

Infliximab versus adalimumab

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 24 months: CDAI=<150 (higher values favour adalimumab)								
1 (Tursi 2014)	RCT	20	RR 1.00 (0.75, 1.34)	Very serious[1]	NA[2]	No serious	Very serious[3]	VERY LOW
Endoscopic remission at 12 months: Rutgeers' score <i2 (higher values favour adalimumab)								
1 (Tursi 2014)	RCT	20	RR 0.89 (0.61, 1.29)	Serious[4]	NA[2]	No serious	Very serious[3]	VERY LOW

1 High risk of bias due to participation and detection bias in subjective outcome (no blinding).
2 Inconsistency not applicable as effect size is from one study.
3 Very serious imprecision as 95% CI crossed two MIDs.
4 Moderate risk of bias due to participation and detection bias (no blinding).

Infliximab versus azathioprine

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Endoscopic remission at 12 months: Rutgeers' score <2 (higher values favour infliximab)								
1 (Armuzzi 2013)	RCT	21	RR 1.67 (0.94, 2.95)	Very serious[1]	NA	No serious	Very serious[2]	VERY LOW

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Clinical remission at 12 months: Harvey-Broadshaw index <8 (higher values favour infliximab)								
1 (Armuzzi 2013)	RCT	21	RR 1.01 (0.76, 1.33)	Very serious[1]	NA	No serious	Very serious[2]	VERY LOW
Withdrawal due to adverse events: 12 month follow-up (lower values favour infliximab)								
1 (Armuzzi 2013)	RCT	21	RR 0.31 (0.01, 6.74)	Very serious[1]	NA	No serious	Very serious[2]	VERY LOW

1. High risk of bias as both participants and personnel were un-blinded.
2. Very serious imprecision as 95% CI crossed two MIDs.

Network meta-analysis

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
Clinical relapse (author defined)								
20	RCT	Serious[1]	No serious	No serious	No serious	2401	See Appendix I	Moderate
Endoscopic relapse (Rutgeert's score < 2)								
16	RCT	Serious[1]	No serious	No serious	No serious	1586	See Appendix I	Moderate
Withdrawal due to adverse events								
17	RCT	No serious	No serious	No serious	No serious	1922	See Appendix I	High

1 Greater than 33% of the studies were at moderate risk of bias.

Appendix I: Network meta-analysis results

General methods

For details of the methods adopted for these analyses, please see Appendix B:

Please refer to the following abbreviations for treatment name:

Abbreviation	Treatment
ADA	Adalimumab
AZA	Azathioprine
BUD	Budesonide
INF	Infliximab
INF+MES	Infliximab with mesalazine
MERC	Mercaptopurine
MES	Mesalazine
MET	Metronidazole (3 months)
MET+ADA	Metronidazole (3 months) with Adalimumab
MET+AZA	Metronidazole (3 months) with Azathioprine
PLA	Placebo
SULPH	Sulfasalazine

One RCT (Caprilli 1994) compared mesalazine with no treatment. The addition of this RCT to the network-meta-analys led to an unstable model and a lack of convergence in treatment comparisons. The committee agreed that placebo and no treatment should not be assessed in the same manner due to a potential placebo effect. For this reason, Caprilli 1994 was removed from the NMA and assessed in pairwise analysis.

Accounting for missing data for relapse outcomes

The approach to reporting outcomes across RCTs varied. In most studies, it was possible to directly extract the number of people who experienced disease relapse at the end of the follow-up period. However, due to loss to follow-up, particularly in trials with larger sample sizes or of longer duration, the outcome of interest (remission or relapse) was unknown in a notable proportion of participants. Only a small number of studies analysed outcomes using survival analysis or reported hazard ratios directly.

For each arm of each trial, the number of people who experienced each of the following outcomes was extracted:

- Remission
- Relapse
- Withdrawal due to adverse events
- Lost to follow-up (any reason)

Attempts were made to quantify the degree of overlap between the latter 2 outcomes and relapse events. For example, in some cases, it was possible to determine if a person experienced relapse prior to being lost to follow-up. Participants who could not be definitively classified as being in remission or relapse were counted as missing. Uncertainty in relative treatment effects induced by missing data was then modelled in the NMA using the approach described in Turner 2015. Briefly, this involved introducing a missingness parameter to model the probability of relapse conditional on being missing and assigning it an uninformative prior. The overall probability of relapse for all randomised participants could then be modelled based on the weighted average of the probability of relapse in missing and observed individuals.

Four studies reported clinical relapse, but not clinical remission: D'Haens 2008; Hellers 1998; McLeod 1995, Rutgeerts 1995 and Wenckert 1977. These studies were included in the NMA and were not analysed in the pairwise analysis for clinical remission. One study (Lopez-Sanroman 2017) did not report clinical relapse and numbers of relapse was calculated. One study (McLeod 1995) did not report withdrawals due to adverse events and this was calculated.

For more information regarding the methods of calculating missing data and accounting for the uncertainty due to missing data, please see the end of Appendix I: Accounting for uncertainty due to missing data.

Withdrawal due to adverse events

For the outcome withdrawal due to adverse events, the reported number of events in the ITT or mITT population was used and no missing values were assumed. Where all arms of the trial reported no withdrawals due to adverse events, the RCT was excluded from the NMA as it did not contribute any evidence. Where at least one arm of the RCT reported events, it was included in the NMA. To account for zero events, 0.5 was added to the numerator and 1 to the denominators of all arms of the RCT.

Model critique: inconsistency checking

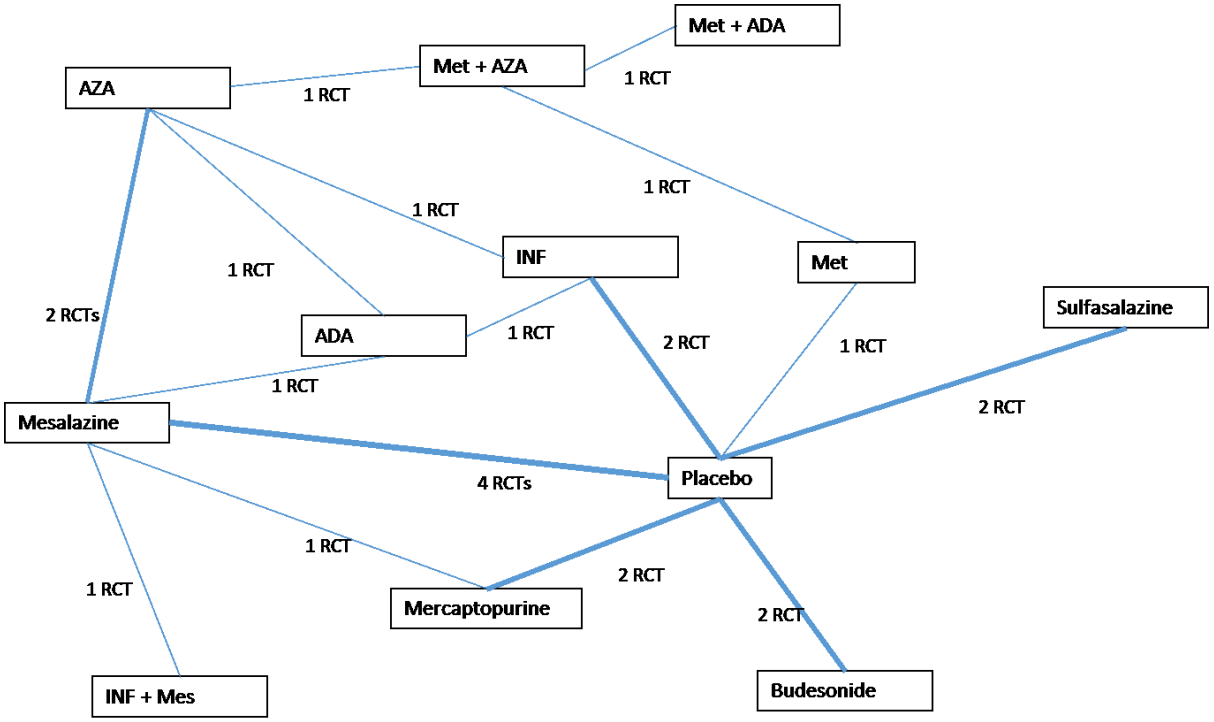
Heterogeneity concerns the differences in treatment effects between trials within each treatment contrast, while consistency concerns the differences between the direct and indirect evidence informing the treatment contrasts (Dias 2011b & 2013).

Inconsistency was assessed by comparing the chosen consistency model (fixed or random effects) to an "inconsistency", or unrelated mean effects, model (Dias 2011b & 2013). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that inconsistency can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 distinct trials (van Valkenhoef 2016).

Outcome: Clinical relapse

Evidence from 20 RCTs on 12 interventions reporting the proportion of people with endoscopic relapse was assessed in an NMA. Convergence was satisfactory for both fixed and random effects models at 30,000 iterations and the models were compared using results based on samples from a further 40,000 iterations on two chains.

Figure 83: Network diagram for clinical relapse as defined by author



Thickness of the line indicates the number of RCTs contributing to the comparison.

Table 17: Model fit statistics for clinical relapse as defined by author

Model	Between study heterogeneity – standard deviation (95%CI)	Total residual deviance[a]	DIC[b]
Fixed effects – consistency	----	Observed values: 37.78 Missing values: 45.16	416.086
Random effects – consistency	0.1476 (0.0155 - 0.561)	Observed: 37.86 Missing: 45.19	417.291
Fixed effect inconsistency	---	Observed: 37.72 Missing: 44.9	418.889

[a] Posterior median residual deviance, in observed and missing values, compared to 42 total data points
[b] Deviance information criteria (DIC) – lower values preferred

No differences were found in model fit for fixed effects and random effects models and the simpler model, fixed effects, was chosen.

Table 18: Input data for clinical relapse as defined by author

Study	Treat 1	Relapses	M	Treat 2	Relapses	M	Treat 3	Relapses	M
Armuzzi 2013[a]	INF	1/11	0	AZA	1/11	1	NA	NA	NA
Brignola 1995[a]	MES	7/44	6	PLA	10/43	4	NA	NA	NA
Ewe 1989[a]	SULPH	42/111	47	PLA	58/121	41	NA	NA	NA
Manosa 2013[a]	MES	1/25	2	AZA	2/25	3	NA	NA	NA
Tursi 2014[a]	INF	1/10	0	ADA	1/10	0	NA	NA	NA
Savarino 2013[b]	ADA	1/16	0	AZA	13/17	0	MES	12/ 18	0
Ardizzone 2004[b]	AZA	12/69	11	MES	20/71	9	NA	NA	NA
Ewe 1999[b]	BUD	8/43	6	PLA	11/40	8	NA	NA	NA
Hanauer 2004[b]	MES	19/44	14	PLA	23/40	12	MERC	24/47	8
Lochs 2000[b]	PLA	50/166	5	MES	36/152	9	NA	NA	NA
Mowat 2016[b]	PLA	26/112	40	MERC	16/128	44	NA	NA	NA
Regueiro 2009[b]	INF	2/11	1	PLA	6/13	0	NA	NA	NA
Regueiro 2016[b]	INF	19/147	44	PLA	29/150	28	NA	NA	NA
Yoshida 2012[b]	INF+ MES	3/15	0	MES	4/16	0	NA	NA	NA
D'Haens 2008[c]	MET+ AZA	3/40	6	MET	7/41	9	NA	NA	NA
Hellers 1999[c]	BUD	20/63	18	PLA	20/66	13	NA	NA	NA
Lopez-Sanroman 2017[c]	MET+ ADA	4/45	3	MET+A ZA	11/39	3	NA	NA	NA
McLeod 1995[c]	MES	27/87	7	PLA	31/76	8	NA	NA	NA
Rutgeerts 1995[c]	MET	9/29	2	PLA	14/28	1	NA	NA	NA
Wenckert 1977[c]	SULPH	4/32	2	PLA	9/34	2	NA	NA	NA

Study	Treat 1	Relapses	M	Treat 2	Relapses	M	Treat 3	Relapses	M

LTFU: loss to follow-up. M: missing; NA: not applicable.
Missing values were calculated in the following manner, in accordance with methods set out in Turner 2015:
[a]*Mutually exclusive events: missing are sum of withdrawal and LTFU.*
[b]*Events are not mutually exclusive: missing are not in relapse or remission.*
[c]*Not calculable - assumed due to LTFU.*

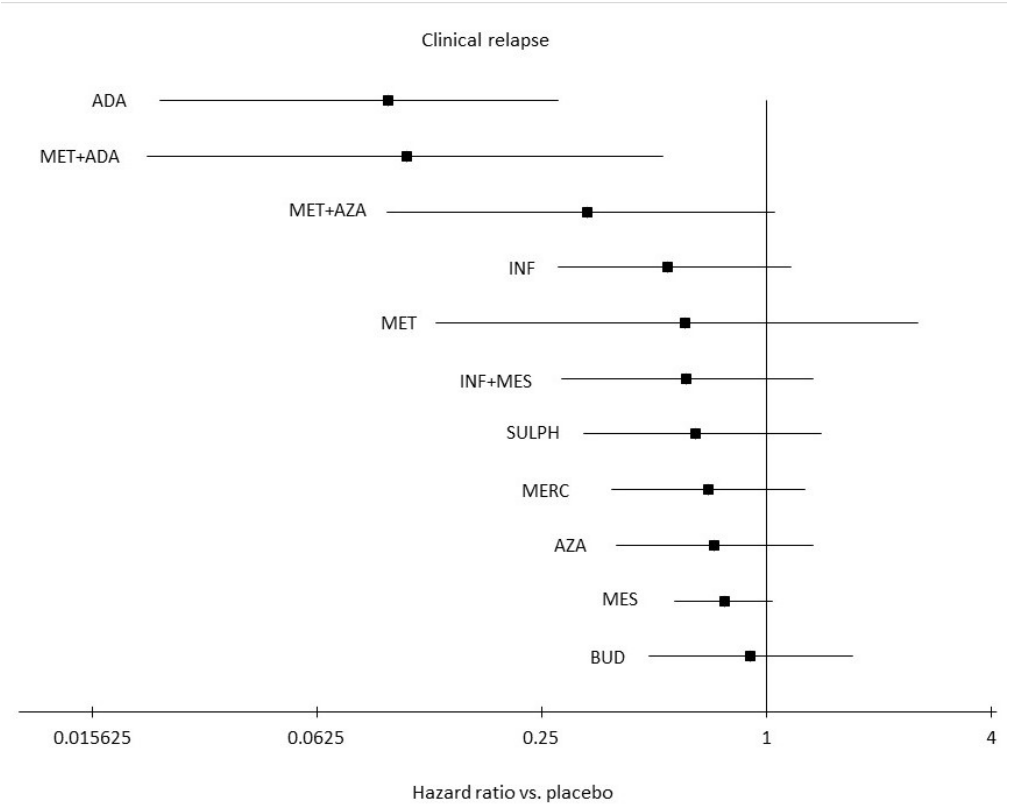
Table 19: Clinical relapse as defined by author: relative effectiveness of all pairwise comparisons

	PLA	ADA	AZA	BUD	INF	MERC	MES	MET	INF+MES	MET+ ADA	MET+ AZA	SULPH
PLA												
ADA	**0.10 (0.02, 0.28)**											
AZA	0.73 (0.40, 1.33)	7.54 (2.58, 31.07)										
BUD	0.90 (0.48, 1.70)	9.37 (2.61, 43.19)	1.23 (0.52, 2.95)									
INF	0.54 (0.28, 1.16)	5.67 (1.70, 26.22)	0.75 (0.32, 1.82)	0.61 (0.24, 1.57)								
MERC	0.70 (0.39, 1.27)	7.32 (2.19, 31.81)	0.96 (0.43, 2.17)	0.78 (0.33, 1.81)	1.29 (0.49, 3.22)							
MES	0.77 (0.57, 1.04)	7.98 (2.83, 32.11)	1.06 (0.62, 1.81)	0.86 (0.42, 1.71)	1.42 (0.65, 2.91)	1.11 (0.59, 2.00)						
MET	0.61 (0.28, 1.34)	6.40 (1.67, 30.37)	0.84 (0.32, 2.13)	0.68 (0.25, 1.84)	1.12 (0.38, 3.15)	0.87 (0.33, 2.35)	0.79 (0.35, 1.81)					
INF+ MES	0.60 (0.13, 2.55)	6.33 (1.01, 45.72)	0.83 (0.17, 3.86)	0.67 (0.13, 3.32)	1.10 (0.20, 5.55)	0.86 (0.17, 4.07)	0.78 (0.18, 3.25)	0.98 (0.18, 5.26)				
MET+ ADA	**0.11 (0.02, 0.53)**	1.16 (0.16, 9.06)	0.15 (0.03, 0.74)	0.12 (0.02, 0.64)	0.20 (0.03, 1.11)	0.16 (0.03, 0.83)	0.14 (0.03, 0.70)	0.18 (0.04, 0.78)	0.18 (0.02, 1.68)			

MET+ AZA	0.33 (0.10, 1.05)	3.48 (0.69, 21.22)	0.45 (0.13, 1.50)	0.37 (0.09, 1.36)	0.60 (0.15, 2.33)	0.47 (0.12, 1.76)	0.43 (0.13, 1.38)	0.55 (0.17, 1.57)	0.55 (0.08, 3.78)	2.98 (1.10, 9.39)		
SULPH	0.65 (0.32, 1.41)	6.76 (1.88, 33.63)	0.89 (0.35, 2.38)	0.72 (0.28, 1.89)	1.19 (0.43, 3.33)	0.92 (0.37, 2.46)	0.84 (0.39, 1.93)	1.06 (0.37, 3.15)	1.09 (0.21, 5.77)	5.98 (1.08, 33.83)	1.95 (0.49, 8.22)	

Values given are hazard ratios. Evidence of a difference, reflected by 95% credible intervals that do not contain the null effect, compared to placebo, are given in bold.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells for pooled direct evidence (fixed-effect pairwise meta-analysis) are not available, as risk ratio of clinical remission was assessed in pairwise meta-analysis, while network meta-analysis assessed the hazard ratio of clinical relapse.

Figure 84: Clinical relapse as defined by author: relative effect of each comparator compared to reference (placebo)

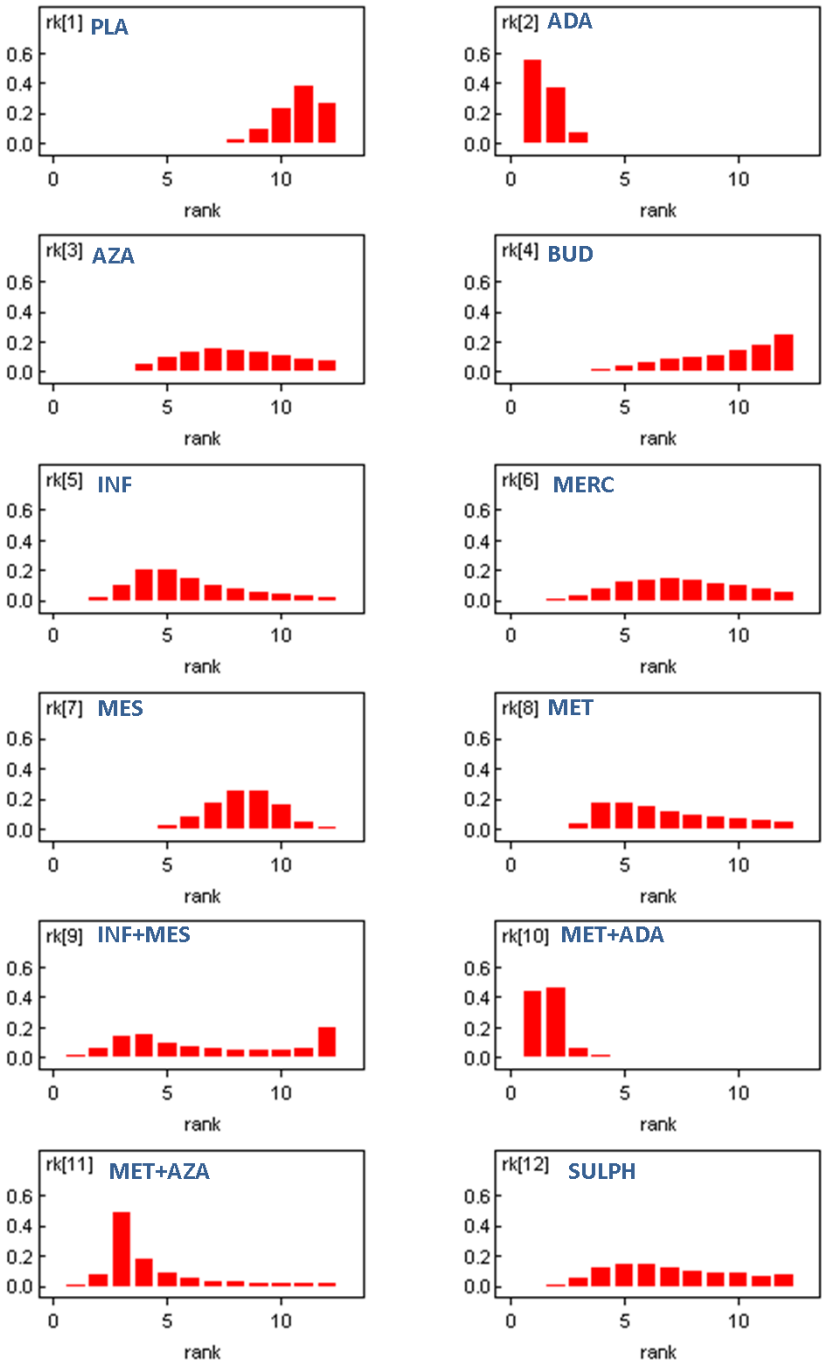


All treatments compared to baseline (null effect when compared to placebo), ordered by rank (treatment with highest probability of reducing relapse (Adalimumab) compared to baseline, to treatment with lowest probability of reducing clinical relapse (Budesonide) compared to baseline. Values less than 1 favour the treatment; values greater than 1 favour baseline. Point estimates are hazard ratios and solid error bars are 95% credible intervals.

Figure 85: Clinical relapse as defined by author: rankings for each comparator

	median rank	Range
ADA	1	(1, 3)
MET+ADA	2	(1, 4)
MET+AZA	3	(2, 11)
INF	5	(3, 11)
MET	6	(3, 12)
INF+MES	6	(2, 12)
MERC	7	(3, 12)
SULPH	7	(3, 12)
AZA	8	(4, 12)
MES	8	(5, 11)
BUD	10	(4,12)
PLA	11	(8, 12)

Figure 86: Clinical relapse as defined by author: rank probability histograms



Probability of each treatment ranking the kth best in reducing <outcome>, where k = 1, …, 12. k=1 is the best rank. Inconsistency checking

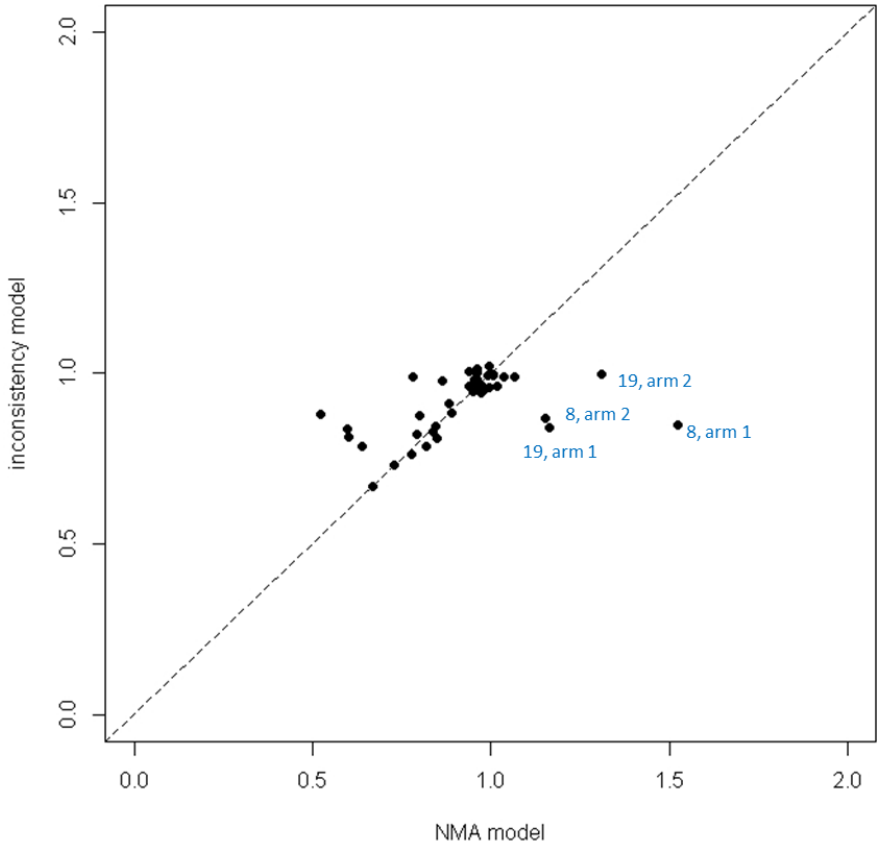
As there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. As the

fixed effects model was preferred, a fixed effects inconsistency model was run. Convergence was satisfactory for this model after 30,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 30,000 iterations on two chains.

When comparing the inconsistency and consistency model (Figure 87), specifically for observed values, one point was found corresponding to the first arm (Adalimumab) of study 8 (Tursi 2014) which had poor fit in the consistency model. This study contributes data to a closed loop: Adalimumab – Infliximab and Azathioprine. Two other studies, Savarino 2013 (study 19) and Armuzzi 2013 (study 8) contribute to this loop. Savarino 2013 shows high benefit of Adalimumab in reducing relapse (r/N = 1/16) compared to Azathioprine (r/N = 13/17), while other comparisons in this loop show no difference in benefit.

In terms of study characteristics, all RCTs included in this loop were unblinded and therefore have high risk of bias for subjective measures, such as clinical relapse. While Savarino 2013 assessed clinical relapse based on CDAI ≥ 150; Armuzzi 2013 and Tursi 2014 were the only two studies which included high-risk populations and used the Harvey-Bradshaw Index (HBI) ≥ 8 to assess relapse. Due to difference in risk and assessment method; a sensitivity analysis removing these two studies from the network was undertaken.

Figure 87: Deviance contributions of observed values for the fixed effects consistency and inconsistency models for clinical relapse



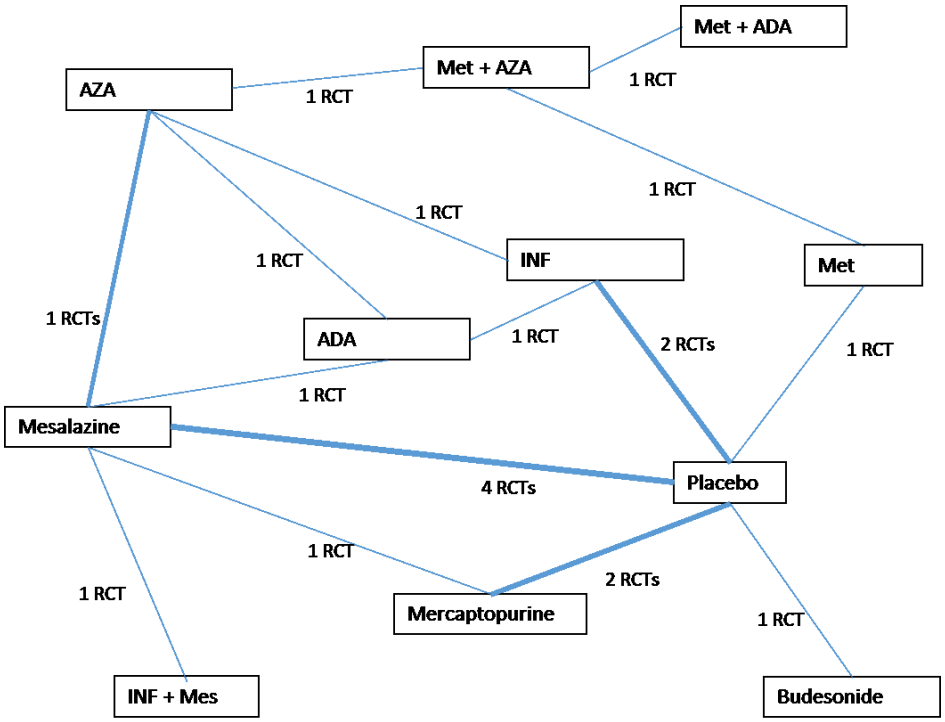
Sensitivity analysis

Two RCTs (Armuzzi 2013 and Tursi 2014) contributed to inconsistency in the NMA model. This could potentially be attributed to both RCTs having high-risk populations and using the HBI scale to assess relapse. A sensitivity analysis was undertaken to remove these 2 RCTs. The sensitivity analysis found no difference in overall results. The committee discussed this inconsistency and noted that the results found from these trials could be representative of the expected clinical benefit of adalimumab, yet the HBI scale is not as widely used as the CDAI score. The committee agreed that these 2 RCTs could contribute important information to the analysis and therefore, they remained in the final NMA.

Outcome: Endoscopic relapse

Evidence from 15 RCTs on 11 interventions reporting the proportion of people with endoscopic relapse was assessed in an NMA. Convergence was satisfactory for both fixed and random effects models at 20,000 iterations and the models were compared using results based on samples from a further 40,000 iterations on two chains.

Figure 88: Network diagram for endoscopic relapse as defined by author



Thickness of the line indicates the number of RCTs contributing to the comparison.

Table 20: Model fit statistics for endoscopic relapse as defined by author

Model	Between study heterogeneity – standard deviation (95%CI)	Total residual deviance[a]	DIC[b]
Fixed effects – consistency	---	Observed: 30.77 Missing: 35.1	280.277
Random effects – consistency	0.350 (0.021 - 1.274)	Observed: 29.41 Missing: 34.59	279.938
Fixed effect inconsistency	----	Observed: 31.8 Missing: 34.65	283.179

[a] Posterior median residual deviance, in observed and missing values, compared to 31 total data points
[b] Deviance information criteria (DIC) – lower values preferred

No differences were found in model fit for fixed effects and random effects models and the simpler model, fixed effects, was chosen.

Table 21: Input data for endoscopic relapse network meta-analysis

Study	Treat 1	Relapses	M	Treat 2	Relapses	M	Treat 3	Relapses	M
Savarino 2013	ADA	1/16	0	AZA	11/17	0	MES	15/18	0
Hellers 1999	PLA	38/66	10	BUD	33/63	14	NA	NA	NA
Regueiro 2009	PLA	11/13	0	INF	1/11	0	NA	NA	NA
Regueiro 2016	PLA	77/150	36	INF	33/147	40	NA	NA	NA
Mowat 2016	PLA	28/112	55	MERC	29/128	61	NA	NA	NA
Brignola 1995	PLA	24/43	4	MES	15/44	5	NA	NA	NA
Lochs 2000	PLA	36/166	94	MES	40/152	91	NA	NA	NA
Rutgeerts 1995	PLA	23/28	0	MET	18/29	6	NA	NA	NA
Tursi 2014	ADA	1/10	0	INF	2/10	0	NA	NA	NA
Armuzzi 2013	AZA	4/11	1	INF	1/11	0	NA	NA	NA
Manosa 2013	AZA	14/25	4	MET+ AZA	9/25	2	NA	NA	NA
Yoshida 2012	MES	13/16	0	INF+ MES	3/15	1	NA	NA	NA

Study	Treat 1	Relapses	M	Treat 2	Relapses	M	Treat 3	Relapses	M
D'Haens 2008	MET	20/41	12	MET+ AZA	14/40	8	NA	NA	NA
Lopez-Sanroman 2017	MET+ ADA	11/45	8	MET+ AZA	8/39	15	NA	NA	NA

NA: not applicable
For studies reporting exclusive events, missing values were assumed to be the sum of both withdrawal due to adverse events and loss to follow-up. In studies where events are not mutually exclusive, missing values = number of people in ITT or mITT population – (number in remission + number in relapse).
Studies with mutual exclusivity: Armuzzi 2013; D'Haens 2008; Lopez-Sanroman 2017; Manosa 2013; Rutgeerts 1995; Tursi 2014; Yoshida 2012.

Hanauer 2004

One included RCT, Hanauer 2004, is a three-arm study comparing Placebo (coded 1), MES (7) and MERC (6). Data for the outcome endoscopic relapse are available on the hazard ratios (HR) and p-values for comparisons of MES and MERC to Placebo. From the available data two log-hazard ratios (lnHR) and their standard errors (se) can be calculated (Table 22).

Table 22: Hanauer 2004 data

	Treatment						
study	arm 1 (Placebo)	arm 2 (MERC)	arm 3 (MES)	$lnHR_{1-6}$	$lnHR_{1-7}$	$se(lnHR_{1-6})$	$se(lnHR_{1-7})$
Hanauer 2004	1	6	7	-0.734	-0.223	0.339	0.295

To calculate the standard error for Placebo – MES, the z-score was approximated from the p-value of 0.458 (Altman and Bland 2005).

To incorporate the HR data into the network meta-analysis model, the covariance between the two lnHR was calculated (Dias et al., 2011 and Woods 2010). This covariance is equal to the variance of log-hazard on the common arm, i.e. the Placebo arm (Franchini et al., 2012) but this is not reported directly in the publication. However, the authors do report the Placebo actuarial rate for endoscopic relapse, obtained from life tables, as 0.64 with 95% confidence interval (0.46 – 0.81). As this interval is approximately symmetric, we assumed that the standard error of this rate can be calculated directly (Collett, 2003) as:

$$SE = \frac{\text{upper bound - lower bound}}{3.92} = 0.08929$$

Based on equations described in Collett (2003), we calculated the required covariance as:

$$\text{var}\left(\log\left(-\log \hat{S}(t)\right)\right) \approx \frac{1}{\left(\log \hat{S}(t)\right)^2 \times \left(\hat{S}(t)\right)^2} \text{var}\left(\hat{S}(t)\right) \quad (1)$$

Using equation (1) we can calculate the required covariance as:

$$\begin{aligned}\mathrm{Cov}\left(\ln HR_{16}, \ln HR_{17}\right) &= \mathrm{var}\left(\log\left(-\log \hat{S}(t)\right)\right) \\ &\approx \frac{1}{\left(\ln 0.64\right)^2 \times 0.64^2} \times 0.08929^2 = 0.097728\end{aligned} \quad (2)$$

As a further check, we know by the Cauchy-Schwartz inequality that:

$$\mathrm{Cov}(X, Y) \leq se(X) \times se(Y)$$

Which in this case means that the required covariance must be less than (or equal to) 0.100005. Therefore the value in equation (2) makes the covariance matrix invertible and can be used as an approximation to the true covariance between the lnHRs.

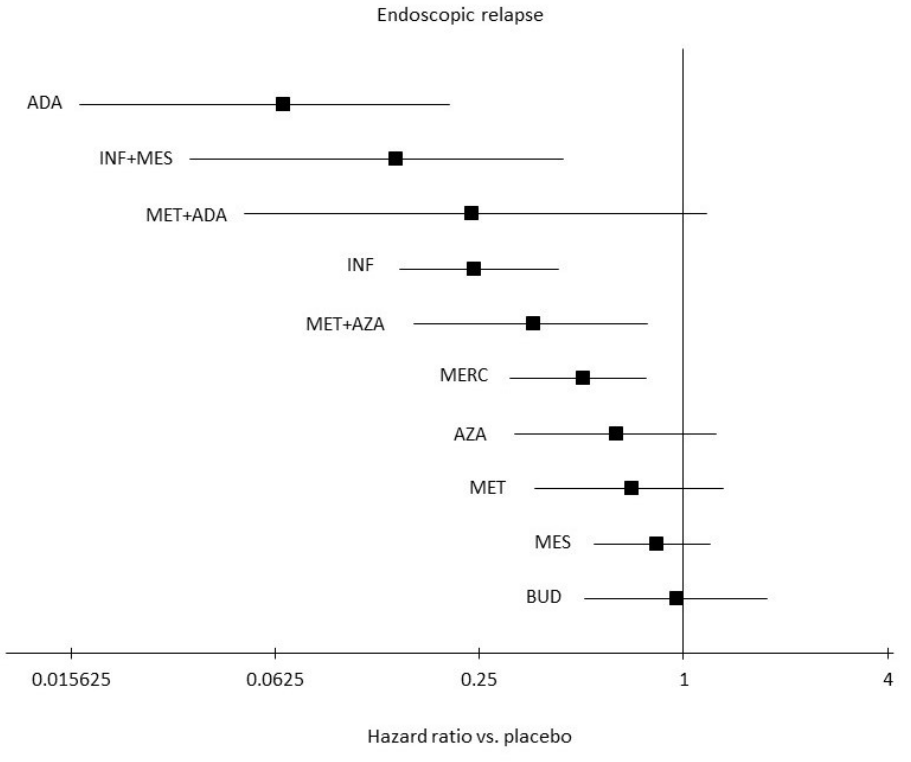
Table 23: Endoscopic relapse: relative effectiveness of all pairwise comparisons

	PLA	ADA	AZA	BUD	INF	MERC	MES	MET	INF+ MES	MET+ ADA	MET+ AZA
PLA											
ADA	**0.07 (0.02, 0.20)**										
AZA	0.64 (0.32, 1.25)	9.71 (3.03, 39.41)									
BUD	0.96 (0.51, 1.77)	14.52 (3.90, 67.81)	1.50 (0.60, 3.78)								
INF	**0.24 (0.15, 0.43)**	3.72 (1.10, 15.37)	0.38 (0.17, 0.87)	0.25 (0.11, 0.59)							
MERC	**0.51 (0.31, 0.78)**	7.65 (2.44, 31.10)	0.79 (0.40, 1.58)	0.53 (0.24, 1.14)	2.08 (0.99, 4.06)						
MES	0.83 (0.54, 1.20)	12.57 (4.08, 50.33)	1.30 (0.68, 2.55)	0.87 (0.42, 1.81)	3.43 (1.70, 6.41)	1.65 (1.43, 1.91)					
MET	0.70 (0.36, 1.32)	10.60 (2.94, 48.43)	1.10 (0.49, 2.46)	0.73 (0.29, 1.81)	2.88 (1.24, 6.42)	1.39 (0.65, 2.94)	0.84 (0.41, 1.73)				
INF+ MES	**0.14 (0.04, 0.44)**	2.15 (0.38, 12.15)	0.22 (0.05, 0.78)	0.15 (0.03, 0.54)	0.58 (0.13, 2.05)	0.28 (0.07, 0.84)	0.17 (0.04, 0.50)	0.20 (0.04, 0.75)			
MET+ ADA	0.24 (0.05, 1.17)	3.75 (0.55, 27.54)	0.38 (0.08, 1.81)	0.25 (0.05, 1.37)	0.98 (0.20, 5.02)	0.48 (0.10, 2.44)	0.29 (0.06, 1.46)	0.34 (0.08, 1.65)	1.72 (0.25, 14.52)		
MET+ AZA	**0.36 (0.16, 0.78)**	5.47 (1.49, 25.35)	0.57 (0.27, 1.15)	0.38 (0.14, 1.02)	1.49 (0.57, 3.69)	0.72 (0.30, 1.66)	0.44 (0.19, 0.98)	0.52 (0.25, 1.06)	2.55 (0.65, 12.32)	1.50 (0.38, 5.51)	

Values given are hazard ratios. Evidence of a difference, reflected by 95% credible intervals that do not contain the null effect, compared to placebo, are given in bold. The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the

shaded cells for pooled direct evidence (fixed-effect pairwise meta-analysis) are not available, as risk ratio of endoscopic remission was assessed in pairwise meta-analysis, while network meta-analysis assessed the hazard ratio of endoscopic relapse.

Figure 89: Endoscopic relapse: relative effect of each comparator compared to reference (placebo)

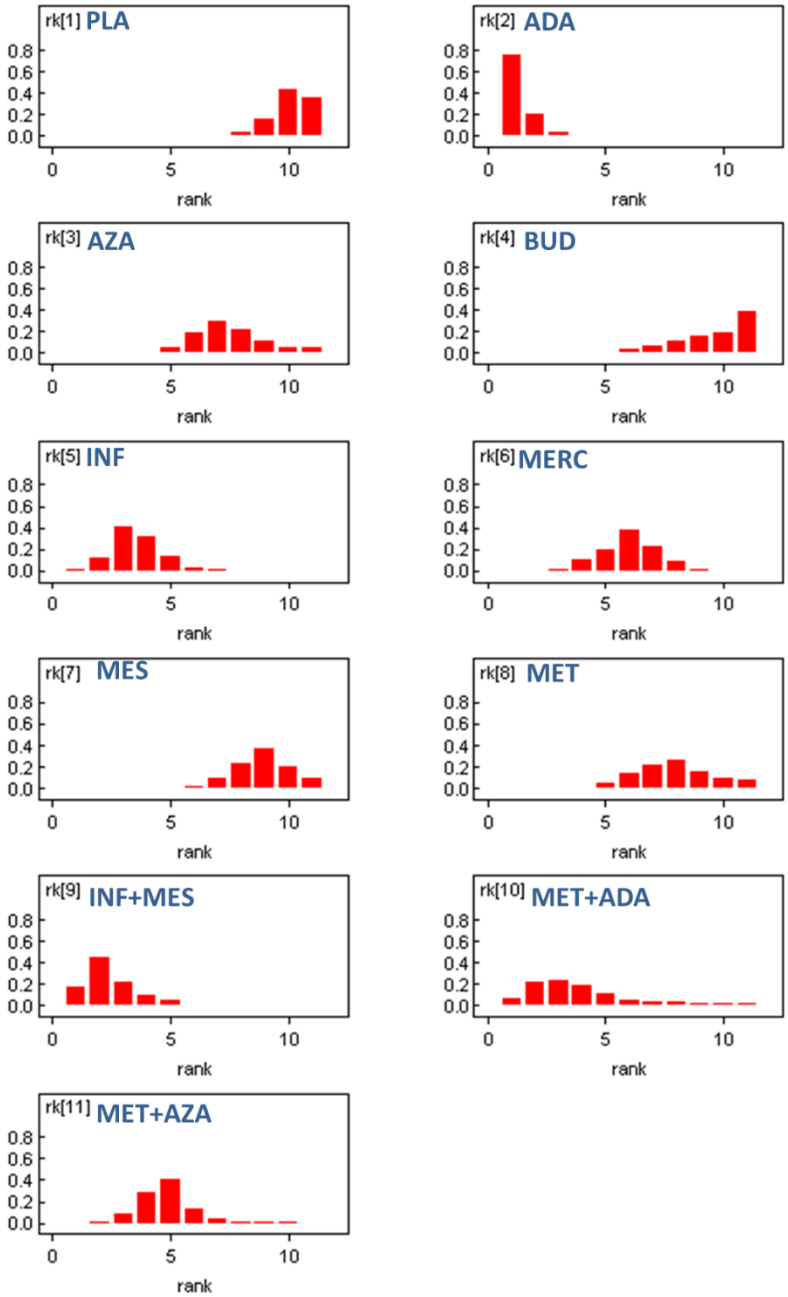


All treatments compared to baseline (null effect when compared to placebo), ordered by rank (treatment with highest probability of reducing endoscopic relapse (Adalimumab) compared to baseline, to treatment with lowest probability of reducing endoscopic relapse (Budesonide) compared to baseline. Values less than 1 favour the treatment; values greater than 1 favour baseline. Point estimates are hazard ratios and solid error bars are 95% credible intervals.

Figure 90: Endoscopic relapse: rankings for each comparator

Treatment	Median rank	Range
ADA	1	(1,3)
INF+MES	2	(1,5)
INF	3	(2,6)
MET+ADA	3	(1, 11)
MET+AZA	5	(3,7)
MERC	6	(4,8)
AZA	7	(5,11)
MET	8	(5,11)
MES	9	(7,11)
PLA	10	(8,11)
BUD	10	(6,11)

Figure 91: Endoscopic relapse: rank probability histograms



Probability of each treatment ranking the kth best in reducing <outcome>, where k = 1, …, 12. k=1 is the best rank.

Inconsistency checking

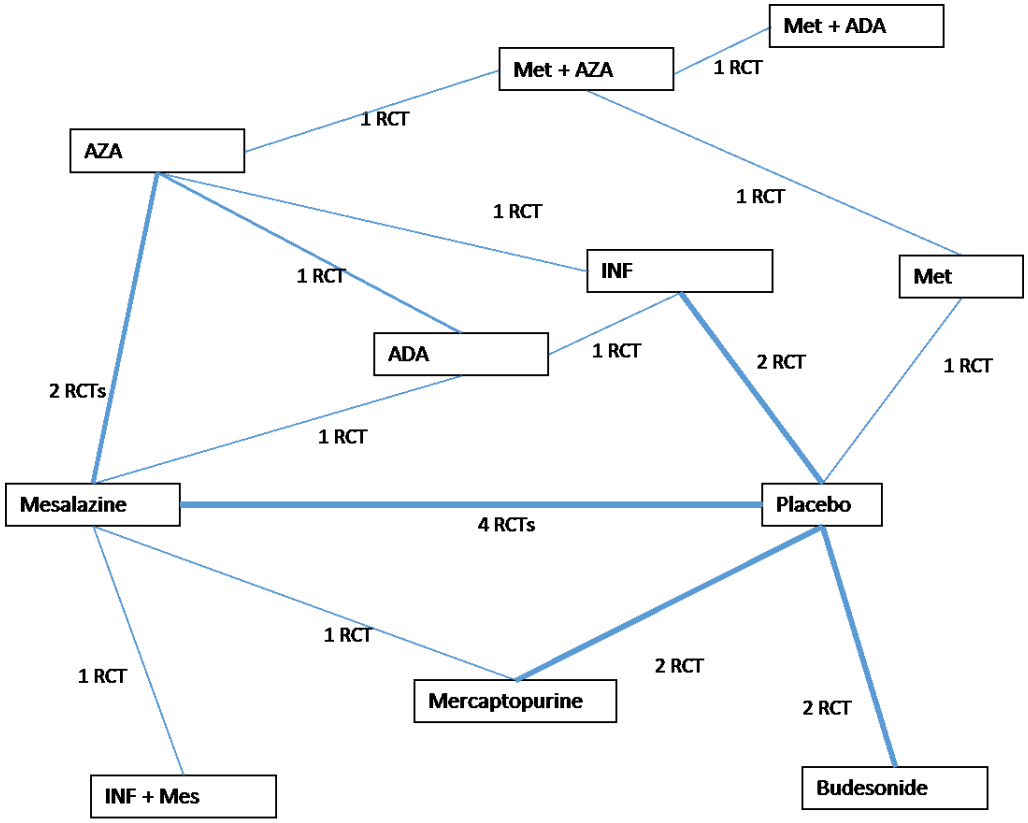
As there were closed loops of direct evidence within the network that were informed by at least 3 distinct sets of trials, inconsistency checks were possible for this outcome. As the fixed effects model was preferred, a fixed effects inconsistency model was run. Convergence was satisfactory for this model after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on

two chains. No evidence of inconsistency was found through comparison of the consistency and inconsistency fixed effects models.

Outcome: Withdrawal due to adverse events

Evidence from 16 RCTs on 11 interventions reporting the proportion of people withdrawing due to adverse events was assessed in an NMA. Convergence was satisfactory for both fixed and random effects models at 20,000 iterations and the models were compared using results based on samples from a further 50,000 iterations on two chains, as the model required more than 40,000 iterations to produce precise estimates (because of high levels of autocorrelation).

Figure 92: Network diagram for withdrawal due to adverse events



Thickness of the line indicates the number of RCTs contributing to the comparison.

Table 24: Model fit statistics for withdrawal due to adverse events

Model	Between study heterogeneity – standard deviation (95%CI)	Total residual deviance[a]	DIC[b]
Fixed effects – consistency	----	35.67	160.863

Model	Between study heterogeneity – standard deviation (95%CI)	Total residual deviance[a]	DIC[b]
Random effects – consistency	0. 4076 (0.02972, 1.315)	31.41	161.442
Random effect inconsistency	0.4814 (0.05165, 1.777)	33.59	165.723
[a] Posterior median residual deviance, in observed and missing values, compared to 34 total data points [b] Deviance information criteria (DIC) – lower values preferred			

There was a lack of convergence in the estimation of treatment effects involving infliximab with mesalazine in the fixed effects model, while convergence was achieved in the estimation of all treatment effects in the random effects model. Additionally, there was no meaningful difference in the DIC between the fixed and random effects models. Due to these reasons, the random effects model was chosen."

Table 25: Input data for withdrawal due to adverse events network meta-analysis

Study	Treat 1	Withdrawals	Treat 2	Withdrawals	Treat 3	Withdrawals
Brignola 1995	PLA	3/43	MES	5/44	NA	NA
Hanauer 2004	PLA	4/40	MERC	9/47	MES	6/44
Ewe 1999	PLA	1/40	BUD	1/43	NA	NA
Hellers 1999	PLA	5/66	BUD	5/63	NA	NA
Regueiro 2009	PLA	1/13	INF	2/11	NA	NA
Regueiro 2016	PLA	19/150	INF	32/147	NA	NA
Mowat 2016	PLA	41/112	MERC	39/128	NA	NA
Rutgeerts 1995	PLA	1/28	MET	5/29	NA	NA
Armuzzi 2013*	AZA	1/11	INF	0/11	NA	NA
Savarino 2013	ADA	1/16	AZA	2/17	MES	2/18
Ardizzone 2004	AZA	15/69	MES	6/71	NA	NA
D'Haens 2008	MET	3/41	MET+ AZA	2/40	NA	NA
Lopez-Sanroman 2017	PLA	1/45	MET+ AZA	9/39	NA	NA
Yoshida 2012*	MES	0/16	INF+ MES	1/15	NA	NA
Manosa 2013*	AZA	1/25	MET+ AZA	0/25	NA	NA
Lochs 2000	PLA	6/166	MES	14/152	NA	NA
NA: not applicable **Where there were 0 events, 0.5 was added to the numerator and 1 to the denominator in both arms of the trial.*						

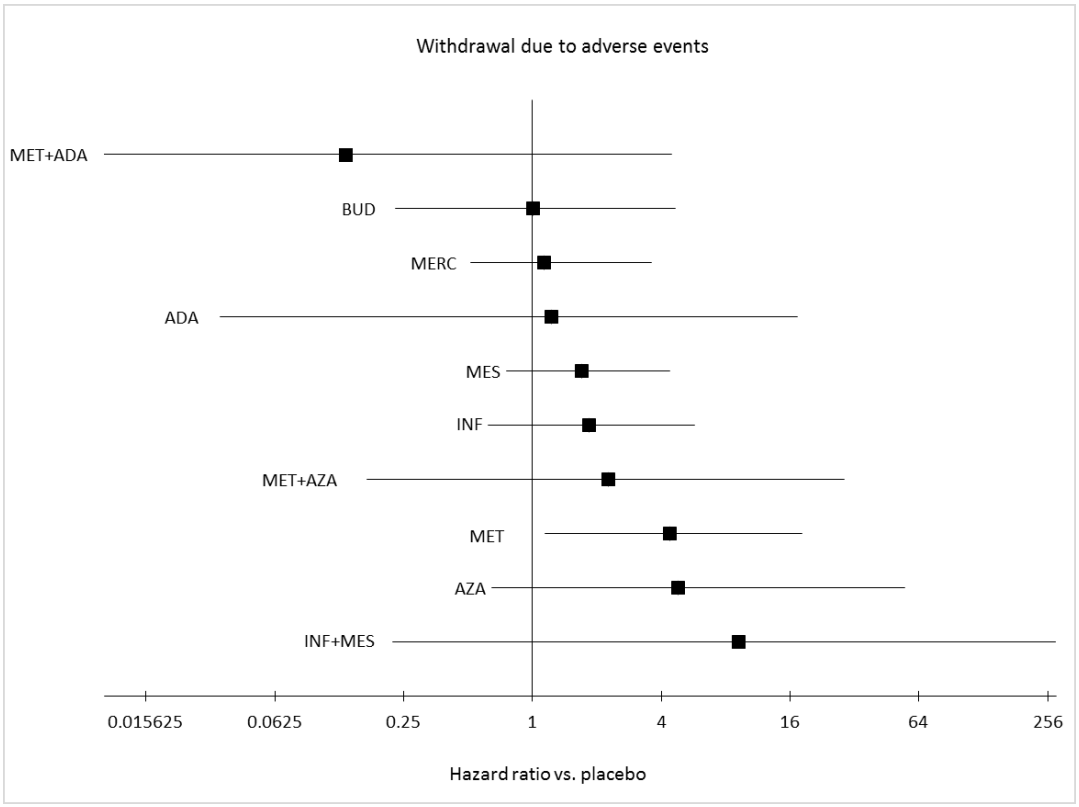
Table 26: Withdrawal due to adverse events: relative effectiveness of all pairwise comparisons

	PLA	ADA	AZA	BUD	INF	MERC	MES	MET	INF+ MES	MET+ ADA	MET+ AZA
PLA											
ADA	1.23 (0.03, 17.39)										
AZA	4.39 (1.15, 18.14)	3.49 (0.31, 110.20)									
BUD	1.01 (0.23, 4.67)	0.86 (0.04, 38.28)	0.23 (0.03, 1.67)								
INF	1.84 (0.62, 5.74)	1.53 (0.09, 58.38)	0.43 (0.08, 2.01)	1.84 (0.29, 11.70)							
MERC	1.13 (0.51, 3.59)	0.97 (0.06, 38.47)	0.27 (0.06, 1.34)	1.13 (0.21, 7.61)	0.62 (0.17, 3.08)						
MES	1.71 (0.76, 4.39)	1.40 (0.11, 45.89)	0.40 (0.12, 1.24)	1.70 (0.31, 10.00)	0.92 (0.25, 3.80)	1.49 (0.44, 4.32)					
MET	4.80 (0.65, 54.80)	4.28 (0.13, 285.20)	1.12 (0.11, 13.76)	4.78 (0.38, 79.80)	2.59 (0.27, 35.53)	4.07 (0.41, 52.72)	2.81 (0.32, 33.00)				
INF+ MES	9.16 (0.22, 4265.00)	8.58 (0.08, 6135.00)	2.13 (0.05, 984.30)	9.05 (0.17, 5108.00)	4.92 (0.11, 2406.00)	7.74 (0.17, 3749.00)	5.25 (0.14, 2347.00)	1.80 (0.03, 1174.00)			
MET+ ADA	0.13 (0.00, 4.46)	0.12 (0.00, 15.16)	0.03 (0.00, 0.98)	0.13 (0.00, 5.92)	0.07 (0.00, 2.75)	0.12 (0.00, 4.05)	0.08 (0.00, 2.61)	0.03 (0.00, 0.56)	0.01 (0.00, 2.01)		
MET+ AZA	2.27 (0.17, 28.70)	1.96 (0.05, 143.10)	0.52 (0.03, 6.45)	2.27 (0.11, 41.98)	1.21 (0.08, 18.68)	1.94 (0.12, 27.69)	1.31 (0.09, 17.44)	0.46 (0.05, 3.46)	0.24 (0.00, 20.29)	16.02 (1.82, 396.60)	

Values given are hazard ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells for pooled direct evidence (fixed-effect pairwise meta-analysis) are not available, as withdrawal due to adverse events were assessed in pairwise meta-analysis

using risk ratios. There was no evidence of a difference, reflected by 95% credible intervals that do not contain the null effect, compared to placebo and one RCT included INF+MES compared to MES reported heterogenous results (large credible intervals).

Figure 93: Withdrawal due to adverse events: relative effect of each comparator compared to reference (placebo)

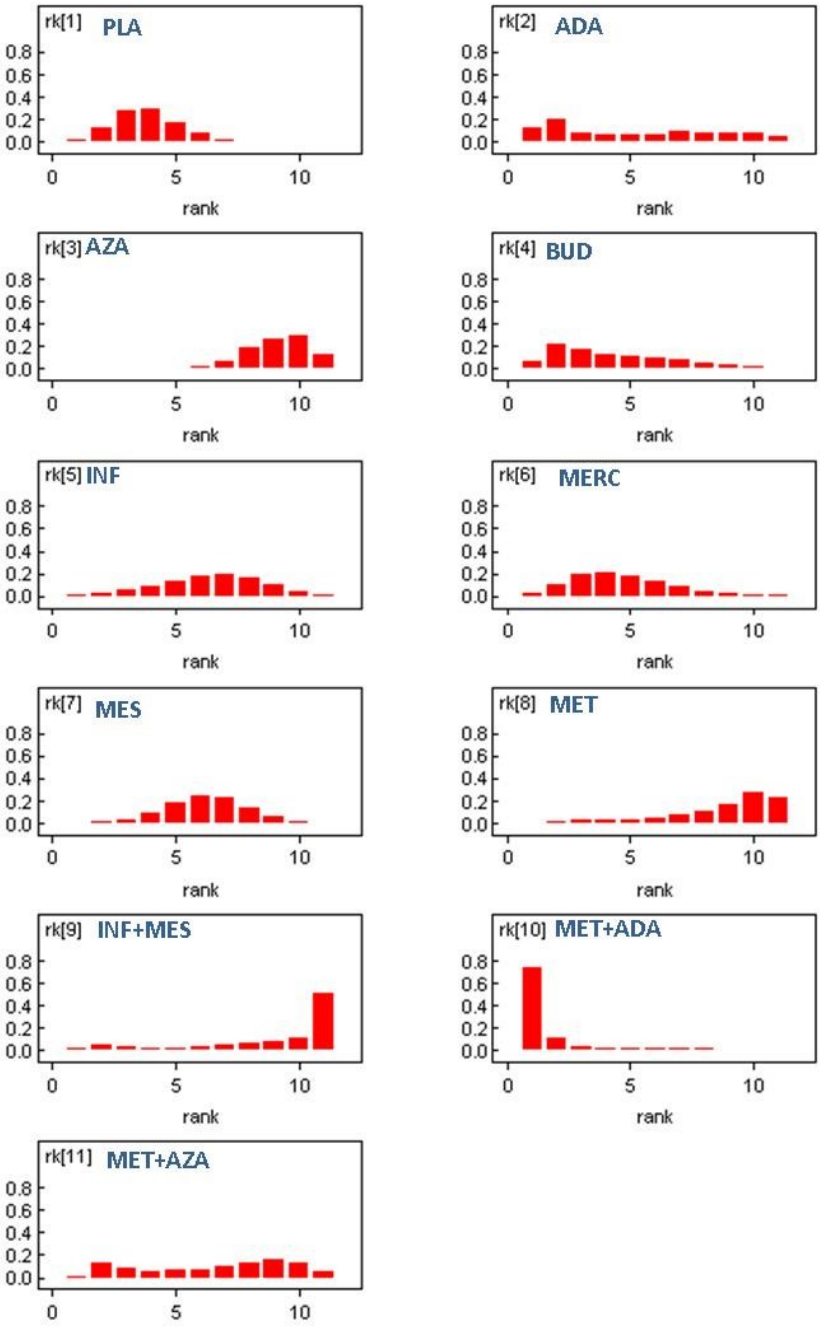


All treatments compared to baseline (null effect when compared to placebo), ordered by rank (treatment with highest probability of reducing withdrawal due to adverse events (Metronidazole (3 months) with adalimumab) compared to baseline, to treatment with lowest probability of reducing withdrawal due to adverse events (Infliximab with mesalazine) compared to baseline. Values less than 1 favour the treatment; values greater than 1 favour placebo. Point estimates are hazard ratios and solid error bars are 95% credible intervals.

Table 27: Withdrawal due to adverse events: rankings for each comparator

Treatment	Median rank	Range
MET+ADA	1	(1,8)
PLA	4	(2,7)
BUD	4	(1,10)
MERC	4	(2, 9)
ADA	5	(1, 11)
MES	6	(3, 9)
INF	7	(2, 10)
MET+AZA	7	(2, 11)
AZA	9	(6, 11)
MET	10	(3, 11)
INF+MES	11	(2, 11)

Figure 94: Withdrawal due to adverse events: rank probability histograms



Probability of each treatment ranking the kth best in reducing <outcome>, where k = 1, …, 12. k=1 is the best rank.

Accounting for uncertainty due to missing data

The following text was provided by the Technical Support Unit (TSU) at The University of Bristol.

Introduction

One of the objectives of this review was to assess the clinical effectiveness of treatments in terms of post-surgical maintenance of remission for at least 12 months. However, there was a mixture of trials included in this review reporting either remission or relapse outcomes. Because patients remain in remission until a relapse occurs, data are in the form of time to event outcomes, where the outcome is relapse. We therefore model relapse rate as the outcome, and patients who do not relapse are still in remission.

Let R_{ik} be the number of people who remained in remission and n_{ik} the number of people randomised to arm n_{ik} of trial i. In trials where the remission status is known among all people in each arm of the trial, the number of people who relapsed (r_{ik}) is

$$r_{ik} = n_{ik} - R_{ik}$$

Similarly, in trials where the relapse status is known among all people in each arm of the trial, the number of people who remained in remission is

$$R_{ik} = n_{ik} - r_{ik}.$$

In some trials, the remission or relapse status was not known among a subset of people that either withdrew due to adverse events or were lost to follow up (LTFU). In some cases it was possible to infer this information from the text. However, where this was not the case, it was not possible to make assumptions about the remission or relapse status in those that withdrew or were LTFU. We therefore used a method to capture the uncertainty due to the missing information proposed for meta-analysis by Turner 2015 extended to NMA by Spineli 2019.

Methods

Data extraction

For given trial i, the reported number of people who remained in remission, R_{ik}, the reported number of people who relapsed, r_{ik}, the reported number of people who withdrew due to adverse events, w_{ik}, the reported number of people who were LTFU, l_{ik}, and the number of people randomised in each trial arm k, n_{ik}, were extracted. Based on these statistics, the numbers of people with missing relapse (and remission) status, m_{ik}, in each trial arm were determined in one of three ways.

(i) In trials where

$$R_{ik} + r_{ik} = n_{ik},$$

the number of people with missing relapse status was recorded as 0, i.e., $m_{ik} = 0$.

(ii) In trials where

$$R_{ik} + r_{ik} + w_{ik} + l_{ik} = n_{ik},$$

the number of people with missing relapse status were calculated as

$$m_{ik} = w_{ik} + l_{ik}.$$

(iii) In other trials where people appeared to be double counted, i.e.,

$$R_{ik} + r_{ik} + w_{ik} + l_{ik} > n_{ik},$$

the number of people with missing relapse status were calculated as

$$m_{ik} = n_{ik} - (R_{ik} + r_{ik}).$$

To illustrate, consider the data in Table 1 below. In Regueiro 2009, $R_{ik} + r_{ik} = 10 + 1 = 11 = n_{ik}$, thus the remission or relapse status is known in those who withdrew and so $m_{ik} = 0$. In D'Haens 2008, $R_{ik} + r_{ik} = 9 + 20 = 29$, which is less than the number of people randomised (($n_{ik} = 41$), and $R_{ik} + r_{ik} + w_{ik} + l_{ik} = 9 + 20 + 3 + 9 = 41 = n_{ik}$, so the number of people with missing relapse status is $m_{ik} = 3 + 9 = 12$. Finally, in Mowat 2016, $R_{ik} + r_{ik} = 29 + 28 = 57$, which is less than the number of people randomised ($n_{ik} = 112$), but $R_{ik} + r_{ik} + w_{ik} + l_{ik} = 29 + 28 + 41 + 55 = 153 > n_{ik}$, so the number of people with missing relapse status is $m_{ik} = 112 - (29 + 28) = 55$.

Table 1: Subset of study data for illustration

Study	Treatment	Remission (R_{ik})	Relapse (r_{ik})	Withdraw due to AE (w_{ik})	LTFU (l_{ik})	n_{ik}
Regueiro 2009	INF	10	1	2	0	11
D'Haens 2008	MET	9	20	3	9	41
Mowat 2016	PLA	29	28	41	55	112

Synthesis Model

Missing Data Model

To account for the missing data, we made use of a pattern-mixture model that was developed for pairwise meta-analysis in a Bayesian framework, and subsequently extended for network meta-analysis [1, 2]. The number of people who relapsed in study i arm k, r_{ik},

conditional on being observed is assumed to have a binomial likelihood, where the denominator is the total number of people observed, $N_{ik} = n_{ik} - m_{ik}$,

$$r_{ik} \sim \text{Binomial}\left(\pi_{ik}^{obs}, N_{ik}\right)$$

where π_{ik}^{obs} is the probability of an event conditional on an individual being observed. The number of people with missing relapse status is also assumed to have a binomial likelihood,

$$m_{ik} \sim \text{Binomial}\left(q_{ik}, n_{ik}\right)$$

where q_{ik} is the probability of being missing. The probability of relapse regardless of whether a participant is observed or missing, π_{ik}^{all}, is a weighted average of the probability of relapse of those who are observed and those who are missing:

$$\pi_{ik}^{all} = q_{ik}\pi_{ik}^{miss} + \left(1 - q_{ik}\right)\pi_{ik}^{obs} \qquad (1)$$

where π_{ik}^{miss} is the probability of relapse in people with missing relapse status. The missingness parameter, π_{ik}^{miss}, can be given either vague or informative priors.

We assumed there was no prior information on the missingness mechanism, other than the probability is constrained between 0 and 1, so π_{ik}^{miss}, was given a Beta(1,1) prior.

The probability of relapse in the observed data is obtained from π_{ik}^{miss} and π_{ik}^{all} by rearranging equation (1) above to give:

$$\pi_{ik}^{obs} = \max\left\{0, \min\left\{1, \frac{\pi_{ik}^{all} - q_{ik}\pi_{ik}^{miss}}{\left(1 - q_{ik}\right)}\right\}\right\}.$$

The relapse probability in all patients, π_{ik}^{all}, is the parameter of interest, and the parameter on which we put the NMA model.

Network Meta-Analysis Model

Since the reported number of people who relapsed is expected to increase with follow-up time, and the trials varied in follow-up time, we modelled the rate of relapse using a cloglog link function (Dias 2011; 2018):

$$\text{c}\log\log\left(\pi_{ibk}^{all}\right) = \mu_i + \delta_{ibk}$$

where μ_i is the study-specific log hazard rate of relapse on the baseline treatment b, and δ_{ibk} is the study-specific log hazard ratio, where

$\delta_{ibk} = d_{bk}$ in the case of a fixed effect model

$\delta_{ibk} \sim \text{Normal}\left(d_{bk}, \tau^2\right)$ in the case of a random effects model

$d_{bk} = d_{1k} - d_{bk}$ is the pooled log hazard ratio for treatment in arm k vs. treatment in arm b [3, 4].

2.2.3 Priors

The study-specific log hazard rates, μ_i, pooled log hazard ratios relative to a reference treatment, d_{1k}, were assigned Normal(0, 10 000) priors, the probability of a participant missing, q_{ik}, was given a Uniform(0,1) prior, and the probability of relapse in people with missing relapse status, π_{ik}^{miss}, was given a Beta(1,1) prior.

References

Dias, S., et al., *NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials*, in *Technical Support Document*. 2011.

Dias, S., et al., *Network meta-analysis for decision making*. Statistics in Practice. 2018, Hoboken, NJ: Wiley.

Spineli, L.M., *Modeling missing binary outcome data while preserving transitivity assumption yielded more credible network meta-analysis results.* Journal of Clinical Epidemiology, 2019. 105: p. 19-26.

Turner, N.L., et al., *A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis.* Statistics in Medicine, 2015. 34: p. 2062-2080.

WinBUGS code

Withdrawal due to adverse events: binomial likelihood, cloglog link (random effects) model

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
model{                                      # *** PROGRAM STARTS
for(i in 1:ns){                             # LOOP THROUGH STUDIES
  w[i,1] <- 0           # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0       # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.0001)                    # vague priors for all trial baselines
  for (k in 1:na[i]){                       # LOOP THROUGH ARMS
  r[i,k] ~ dbin(p[i,k],n[i,k])              # Binomial likelihood
  cloglog(p[i,k])<- mu[i] + delta[i,k]      # model for linear predictor
  rhat[i,k] <- p[i,k] * n[i,k]              # expected value of the numerators
  # Deviance contribution
  dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
```

```
  resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this
trial
  for (k in 2:na[i]){                        # LOOP THROUGH ARMS
  delta[i,k] ~ dnorm(md[i,k],taud[i,k])    # trial-specific LOR distributions
  # mean of LOR distributions (with multi-arm correction)
  md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
  taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm
correction)
  w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
  sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
   }
 }
totresdev <- sum(resdev[])                   # Total Residual Deviance
d[1] <- 0                     # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }    # vague priors for treatment effects
sd ~ dunif(0,5)
                             # vague prior for between-trial SD
tau <- pow(sd,-2)                                # between-trial precision =
(1/between-trial variance)
# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
    hr[c,k] <- exp(d[k] - d[c])
    lhr[c,k] <- (d[k]-d[c])
   }
 }
# ranking on relative scale
for (k in 1:nt){
#  rk[k] <- nt+1-rank(d[],k)              # assumes events are "good"
  rk[k] <- rank(d[],k)                   # assumes events are "bad"
  best[k] <- equals(rk[k],1) # calculate probability that treat k is best
  # calculates probability that treat k is h-th best
  for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
 }
}
```

Clinical and endoscopic relapse: binomial likelihood, cloglog link (fixed effects) with missing data model

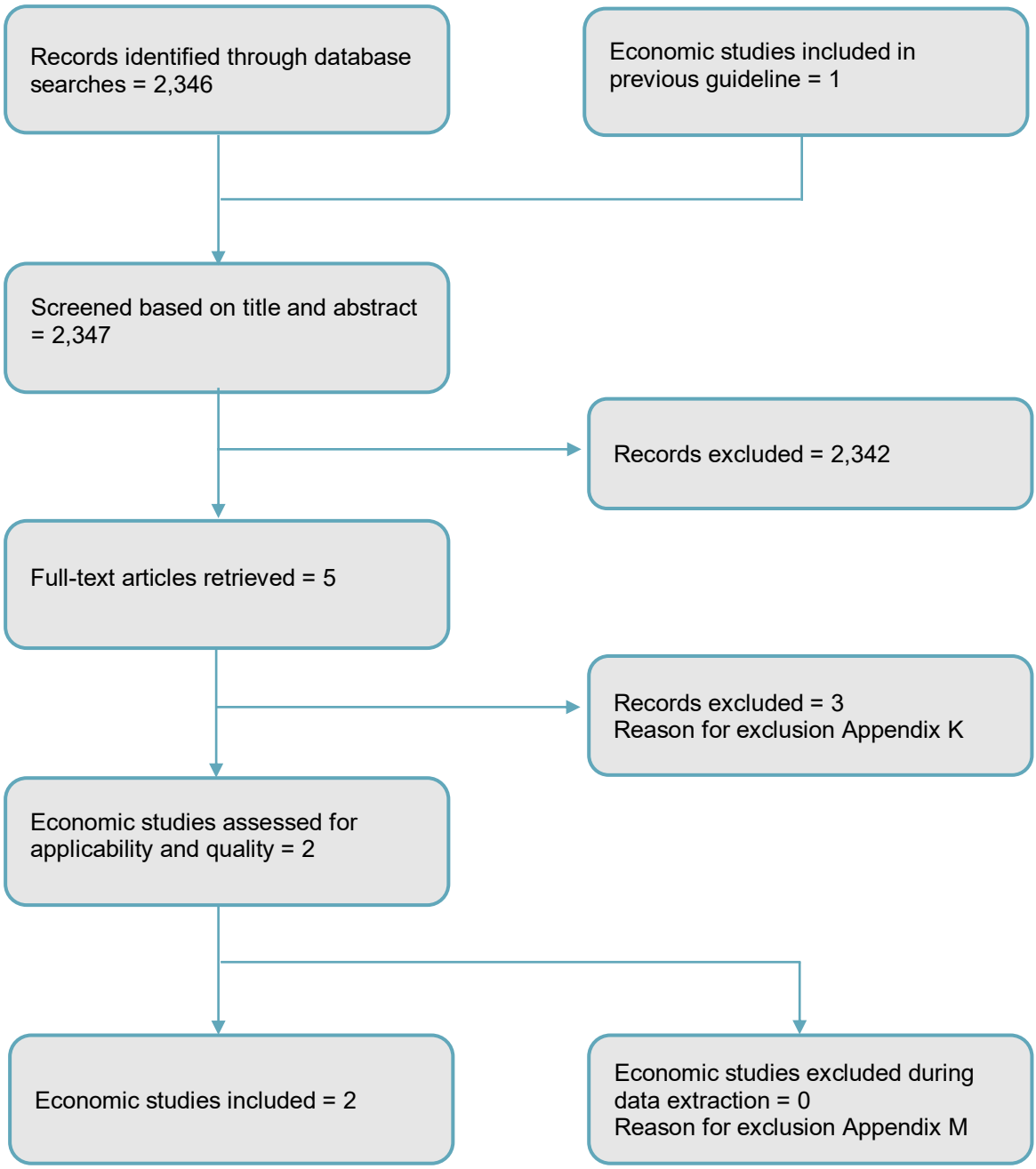
```
# Binomial likelihood, cloglog link, network meta-analysis
# Fixed effects model for multi-arm trials
# with missing data model on Pr(event|missing)

model{                                    # *** PROGRAM STARTS
for(i in 1:ns){                           # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)                  # vague priors for all trial baselines
  for (k in 1:na[i]){                     # LOOP THROUGH ARMS
    N[i,k] <- n[i,k] - m[i,k]             # complete cases
    r[i,k] ~ dbin(p.obs[i,k],N[i,k]) # binomial likelihood for complete cases
    m[i,k] ~ dbin(q[i,k], n[i,k])  # binomial likelihood for missing data
    cloglog(p.all[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]  # model for linear
predictor
    # truncation to ensure probability in (0,1)
    x[i,k] <- (p.all[i,k]-q[i,k]*p.mis[i,k])/(1-q[i,k])
    p.obs[i,k] <- max(0,min(1,x[i,k]))  # pr(event|observed)
    # prior distributions for missing parameters
```

```
    p.mis[i,k] ~ dbeta(1,1)                    # pr(event|missing)
    q[i,k] ~ dunif(0,1)                        # pr(missing)
    # Deviance for observed events
    rhat.obs[i,k] <- p.obs[i,k] * N[i,k] # expected value of the numerators
    # Deviance contribution
    dev.obs[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat.obs[i,k]))
        +  (N[i,k]-r[i,k]) * (log(N[i,k]-r[i,k]) - log(N[i,k]-rhat.obs[i,k])))
    # Deviance for missing data
    rhat.mis[i,k] <- q[i,k] * n[i,k] # expected value of the numerators
    # Deviance contribution
    dev.mis[i,k] <- 2 * (m[i,k] * (log(m[i,k])-log(rhat.mis[i,k]))
        +  (n[i,k]-m[i,k]) * (log(n[i,k]-m[i,k]) - log(n[i,k]-rhat.mis[i,k])))
   }
  # summed residual deviance contribution for each trial
  resdev[i,1] <- sum(dev.obs[i,1:na[i]])  # observed events
  resdev[i,2] <- sum(dev.mis[i,1:na[i]])  # missing data
}
# Total Residual Deviance
totresdev[1] <- sum(resdev[,1])   # observed events
totresdev[2] <- sum(resdev[,2])   # missing data
d[1]<- 0              # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
#
# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
    hr[c,k] <- exp(d[k] - d[c])
    lhr[c,k] <- (d[k]-d[c])
   }
 }
# ranking on relative scale
for (k in 1:nt){
#  rk[k] <- nt+1-rank(d[],k)             # assumes events are "good"
  rk[k] <- rank(d[],k)                  # assumes events are "bad"
  best[k] <- equals(rk[k],1)            # calculate probability that treat k is
best
  # calculates probability that treat k is h-th best
  for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
 }

}
```

Appendix J: Economic evidence study selection



Appendix K: Health economic evidence profiles

Study: Ananthakrishnan 2011				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Decision analytic model **Approach to analysis:** Decision tree. All patients started in a surgical remission state and received one of the interventions. The therapy could be replaced if intolerance developed and replaced or increased if relapse occurred. Possible health states were remission, relapse, repeat surgery and death. Patients in the tailored INF had colonoscopy at 6 months if no previous relapse. No treatment was offered if Rutgeerts i0-i1, otherwise INF was offered (high risk). **Perspective:** US third party payer (all treatments and health state costs but no indirect costs)	**Population:** 35-year-old adults in clinical remission after first ileocecal resection. **Intervention 1:** - No treatment (no treatment started immediately postoperatively) **Intervention 2:** - Azathioprine (AZA) **Intervention 3:** - Metronidazole (MET) **Intervention 4:** - Upfront infliximab (INF) **Intervention 5:** - Tailored infliximab (INF) initiation of INF on patients with severe endoscopic recurrence at 6 months.	**Total costs (mean per patient):** **Base case** Untreated: $3,924 (£2,980) AZA: $3,218 (£2,444) MET: $2,840 (£2,113) Upfront INF: $22,145 (£16,818) Tailored INF: $8, 030 (£6,099) **Currency & cost year:** US dollars 2010[(a)] **Cost components incorporated:** average wholesale drugs cost, costs of drug infusion, monthly costs of remission, active disease, severe active disease (months before reoperation), reoperation costs	**QALYs (mean per patient):** Base-case (recurrence rate 0.24) Untreated: 0.805 QALY AZA: 0.814 QALY MET: 0.821 QALY Upfront INF: 0.828 QALY Tailored INF: 0.821 QALY	**Full incremental analysis:** Base case (relapse rate 0.24) MET is the most cost-effective strategy. ICER upfront INF vs MET: $2,719,014 (£2,065,005)/QALY **Analysis of uncertainty:** Low risk (relapse rate 0.10) MET was the most cost-effective stratregy, ICER: $75,172 (£57,091)/QALY High risk (relapse rate 0.49) MET dominates all strategies with exception of upfront IFX which is not cost-effective, ICER: $1,289,929 (£979,660)/QALY Very high risk (relapse rate 0.78) MET dominates all strategies with exception of upfront IFX which is not cost-effective, ICER: $722348 (£548,600)/QALY Reducing INF cost to $500 (£372) produced an ICER of $74,370/QALY (£56,482/QALY) compared vs. no treatment.

Time horizon: 1 year (Model extended to 3 years). **Discounting:** Discounting was not applied as time horizon was 1 year.				Time horizon extended to 3 years: upfront INF was most effective strategy with an ICER of $1,352,693/QALY (£1,027,327). MET remained the most cost-effective strategy.
Data sources				
Health outcomes: Rate of relapse of no treatment was sourced from Renna (2008, The efficacy of MET and AZA from a Cochrane review (Doherty 2009) Relapse in high and low endoscopic risk from Rutgeerts (1990) Probability of death from US lifetables (uniform across treatment arms) (Lichtenstein 2006) Efficacy of AZA and INF in treating recurrence from ACCENT1 trial Hanauer (2002) for INF and Candy (1995) for ADA Cessation of therapy due to adverse events from meta-analysis (Peyrin-Biroulet 2009) or trials (Rutgeerts 1995, Rutgeerts 2005, Hanauer 2002) Reoperation rate in Wolters (2006) **Quality of life weights:** Health utilities from Lindsay (2008) **Costs:** costs in 2010 US dollars, average wholesale drug costs form 2010 Drug Topic Red Book (2010). Cost of AZA is based on 150 mg dose. Infusion costs from previous model (Kaplan 2007) and adjusted for inflation to 2010 US dollars using the healthcare component of the consumer price index. Monthly cost of remission and active disease from Malone (2010). Cost of surgery from previous Markov model (Silverstein 1999).				
Overall applicability: Partially applicable[(b)] **Overall quality**: Potentially serious limitations[(c)]				
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; RCT, randomised controlled trial				

(a) *Costs converted from 2010 US dollar using a conversion factor of 0.70 and an implied inflation factor of 1.08 (EPPI centre converter)*
(b) *Addresses a similar population and intervention but conducted from US perspective; some drug costs reported are higher than in the current UK context.*
(c) *Study does not compare all available therapies and is limited to 1 year time-horizon. The estimates of relative effectiveness for metronidazole and azathioprine were based on pairwise meta-analyses while the efficacy of infliximab was based on 1 small trial and subject to strong assumptions by the authors. No probabilistic sensitivity analysis was conducted.*

Study: Doherty 2012				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: cost-utility analysis **Study design:** Decision tree **Approach to analysis:** Hypothetical cohort of 100,000 patients commenced on one of four strategies. At the end of 1 year patients could be in one of 2 states: remained in clinical remission for 1 year or experienced clinical recurrence at some point. Transitions were assumed to occur halfway through the year. **Perspective:** Societal perspective (according to authors but only direct medical costs included) **Time horizon:** 1 year (for QALY outcome), 5 years using prevention of endoscopy as an outcome in an exploratory analysis **Treatment effect duration:** 1 year (base case)	**Population:** adults with Crohn's disease treated by surgical resection. Mean age 35 years, duration of disease prior to surgery <10 years. **Intervention 1:** No treatment **Intervention 2:** Mesalamine (MES) (3 g/day) **Intervention 3**: Azathioprine (AZA) (2.5 mg/kg/day) **Intervention 4**: Infliximab (INF) (induction dose at 0, 2 and 6 weeks) and then maintenance therapy every 8 weeks (5mg/kg for 75Kg adult)	**Total costs (mean per patient):** **No treatment**: $1,957 (£1,486) **MES**: $5,904 (£4,484) **AZA**: $6,692 (£5,082) **INF**: Infliximab $25,127 (£19,083) **Currency & cost year:** US dollars 2010[(a)] **Cost components incorporated:** Direct medical treatment costs. Costs of standard follow-up and adverse events were assumed to be similar between strategies and were not modelled.	**QALYs (mean per patient):** **No treatment**: 0.84 **MES**: 0.85 **AZA**: 0.86 **INF**: 0.87	**Full incremental analysis[(b)]:** 1 Year analysis No treatment was the most cost-effective strategy. ICER AZA vs. no treatment: $236,750 (£179,804)/QALY ICER INF vs. AZA: $1,843,500 (£1,400,080) **Analysis of uncertainty:** 5-Year analysis No treatment remaind the most cost-effective strategy. ICER MES: $231,975 (£176,178)/QALY ICER INF: $964,400 (£732,431)

Discounting: No discounting (1-year analysis). Costs and QALY were discounted at a 3% rate from the 5-year exploratory analysis.				
Data sources				
Health outcomes: Effectiveness no therapy, mesalazine and azathioprine/mercaptopurine from meta-analysis of RCTs (Doherty 2009) Effectiveness infliximab from Regueiro 2009. Probability of drug related adverse events assumed to be zero in no treatment group. For mesalazine and azathioprine/mercaptopurine values adopted from Doherty 2009. For Infliximab sourced from Regueiro 2009 and Hanauer 2002. **Quality of life weights:** From standard gamble data derived from cohort of 180 patients with CD (Gregor 1997). Disutilities from adverse events from Chung 2000 and expert opinion. **Costs:** Cost of mesalazine, azathioprine and infliximab were average wholesale price. Medical cost of relapse from Kappelman 2008 and Malone 2010.				
Overall applicability: Partially applicable[(a)] **Overall quality**: Potentially serious limitations[(b)]				

(a) Costs converted from 2010 US dollar using a conversion factor of 0.70 and an implied inflation factor of 1.08 (EPPI centre converter)
(b) Full incremental analysis calculated by the analyst
(c) Does not compare all available treatment options, US perspective.
(d) Structure of the decision tree required strong assumptions to be made about the timing of relapses that may not reflect the natural course of the disease. Efficacy data based on pairwise meta-analysis and one small RCT for infliximab. Cost of reoperation not included.

Appendix L:Health economic analysis

Introduction

A review of the literature identified 2 published economic evaluations that compared treatments for post-surgical maintenance of remission in Crohn's disease. The base case analyses for both of these models adopted a time horizon of 1 year and used clinical relapse as the main outcome of interest. Neither study was conducted from a UK NHS perspective. In order to address these limitations, an original economic model was developed for this review question. The estimates of effectiveness in this original economic model are informed by the results of the network meta-analyses presented in Appendix I and take into account new evidence that has been identified in relation to treatment options to maintain remission in the post-surgical setting since the 2012 Crohn's disease guideline.

Methods

Overview

The model was constructed as a cost-utility analysis from a UK NHS/personal social services perspective with a 3-year time horizon. The time horizon was chosen because it reflected the longest duration of follow-up across a number of RCTs included in the evidence review. The committee was uncertain if the relative treatment effects reported in RCTs could be extrapolated beyond 3 years but also felt it was important for the model to consider the impact of downstream costs and health effects in people who relapsed while on treatment for post-surgical maintenance of remission. The impact of a longer time horizon was explored in scenario analyses. Costs were reported in GBP (£) and health outcomes reported as quality-adjusted life years (QALYs), both discounted at an annual rate of 3.5%.

Population

Adults who have undergone complete macroscopic resection of ileocolonic Crohn's disease in the preceding 3 months. There was insufficient clinical evidence to conduct a separate cost-effectiveness analysis in children.

Comparators

The economic model compares a no treatment strategy and 10 drugs or combinations of drugs for which RCTs were identified in the clinical evidence review and reported the outcome endoscopic relapse (defined as a Rutgeerts' score ≥i2):

1. No treatment
2. Adalimumab
3. Azathioprine
4. Budesonide
5. Infliximab
6. Mercaptopurine
7. Mesalazine
8. Metronidazole

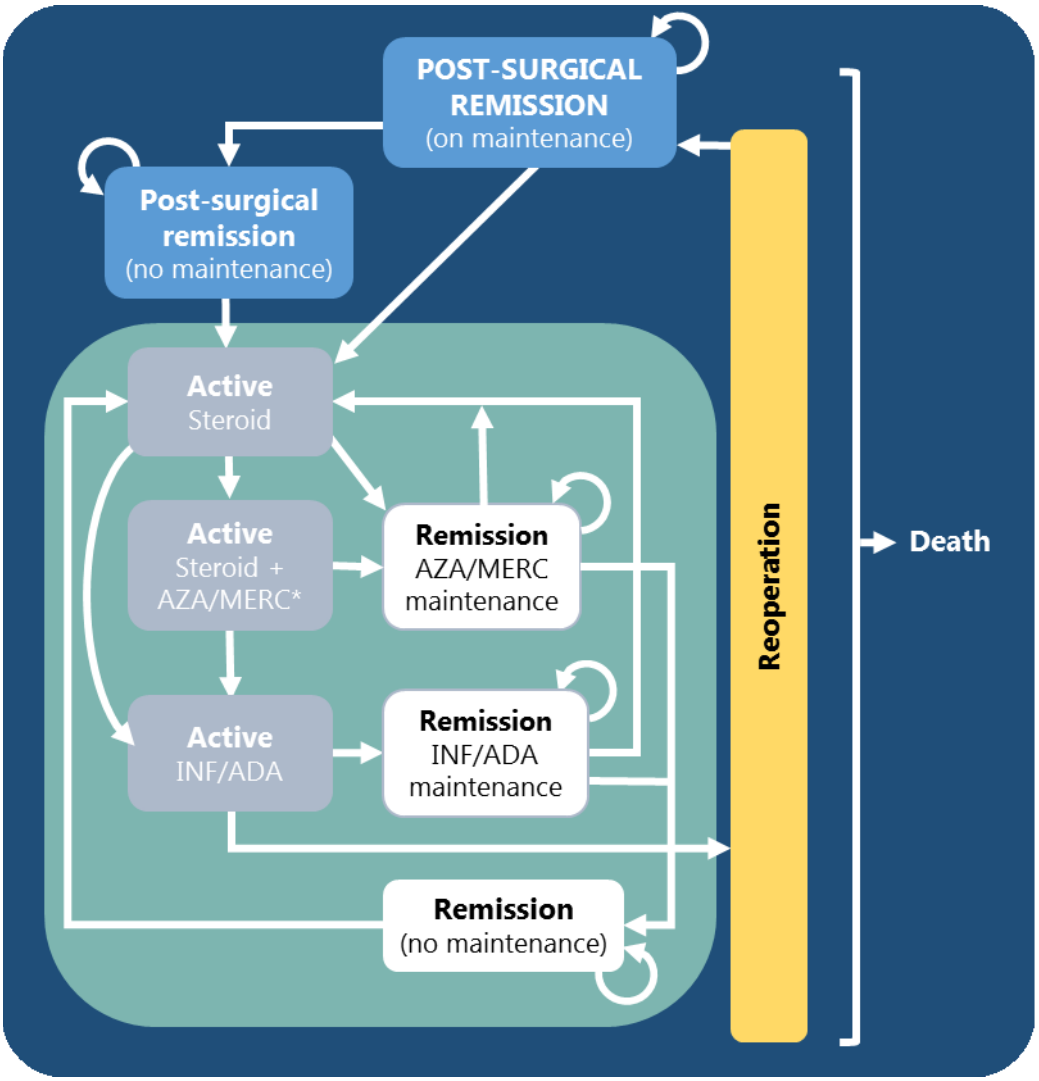
9. Infliximab + mesalazine (INF+MES)
10. Metronidazole + adalimumab (MET+ADA)
11. Metronidazole + azathioprine (MET+AZA)

A scenario analysis was conducted using clinical relapse as the main outcome in the economic model, for which evidence on 1 additional drug, sulfasalazine, was available.

Model structure

A Markov model was used to represent the chronic relapsing-remitting nature of Crohn's disease. A cycle length of 2 months was deemed granular enough to capture clinically relevant state transitions in the model and to account for associated costs and utilities. The basic structure of the model is shown in Figure 95.

Figure 95: Overall structure of the Markov model



The health states post-surgical remission (on maintenance) and remission INF/ADA maintenance were modelled as tunnel states. The green area highlights downstream events in the model informed by recommendations made elsewhere in the 2012 guideline for induction of remission and maintenance of medically-induced remission. AZA = azathioprine; MERC = mercaptopurine; INF = infliximab; ADA = adalimumab

Post-surgical maintenance of remission

The cohort is assumed to start in the post-surgical remission (on maintenance) state receiving one of the strategies listed above. In the model, the initial post-surgical remission (on maintenance) state was split into tunnel states to allow the baseline rate of relapse to vary over time. From this initial state, people can remain in remission, withdraw from post-surgical maintenance treatment or experience disease relapse. For people who withdraw from post-surgical maintenance treatment, their disease is initially assumed to be in remission but they face a higher rate of relapse associated with no post-surgical maintenance treatment.

Induction of remission following relapse and maintenance treatment following medically-induced remission

People whose disease relapses while on post-surgical maintenance treatment are assumed to require further treatment to induce remission as described in the 2012 guideline. In the first instance, people would receive a conventional glucocorticosteroid for one cycle. If remission is achieved with a glucocorticosteroid, the model assumes everyone will receive azathioprine or mercaptopurine as maintenance treatment. If remission is not achieved with a glucocorticosteroid, the model assumes azathioprine or mercaptopurine would be added to the glucocorticosteroid in the next cycle. However, for people whose disease relapsed while receiving azathioprine or mercaptopurine as post-surgical treatment for maintenance of remission, it is unlikely that the same drug would be used again to induce remission so in a scenario analysis, it was assumed these people would receive methotrexate instead. People whose disease does not respond to immunosuppressive and glucocorticosteroid treatment are assumed to receive either infliximab or adalimumab. People whose disease responds to infliximab or adalimumab after one cycle are assumed to remain on treatment for 12 months in the base case. A scenario analysis was run in which people were assumed to continue biologic therapy beyond 12 months for as long as their disease remained in remission.

Reoperation and death

In the model, people whose disease does not respond to infliximab or adalimumab are assumed to undergo reoperation. In the base case, it was assumed that following reoperation, people would return to the same post-surgical maintenance strategy that they received at the start of the model.

Evidence from a matched cohort study of people with inflammatory bowel disease using the UK Clinical Practice Research Datalink cohort showed that Crohn's disease is associated with an increased risk of death (Chu 2017). This was incorporated in the economic model by applying the excess mortality risk for Crohn's disease to general population mortality rates from age-specific life tables for England and Wales (2015-17). It was assumed that the starting age of the cohort was 35 years. Differences in treatment-specific mortality rates were not modelled because this outcome was not reported in most of the trials that were included in the evidence review.

Model parameters

General approach

Estimates of the effectiveness of treatments for post-surgical maintenance of remission were based on the systematic review and network meta-analyses reported in Appendix I. For

downstream events in the model such as the induction of remission following relapse, effectiveness inputs were sourced from the evidence reviews and economic models that were developed for the 2012 guideline. No systematic searches for new evidence were carried out for these parameters. For all other parameters in the model, informal searches were conducted in a variety of databases including Medline (via Pubmed), Google Scholar, the Cost-effectiveness Analysis (CEA) Registry and health economic databases from Sheffield and York Universities. In addition, as part of the systematic review of published economic evaluations for this review question, articles that did not meet formal inclusion criteria but appeared to be relevant to the decision problem were retrieved and the reference lists of these articles were scanned to identify other potentially relevant sources of inputs for the model.

Clinical outcomes

Baseline rate of relapse

The baseline rate of relapse for the no treatment strategy in the economic model was derived from a prospective cohort study (Rutgeerts 1990). This study characterised the natural course of disease recurrence in 89 people who were not receiving any treatment following ileal or ileocolonic resection for Crohn's disease. The study reported the number of people who experienced endoscopic relapse in years 1 and 3 following surgery and the number of people who experienced clinical relapse in years 1, 2 and 3 following surgery. For endoscopic relapse, the authors reported that 65 of 89 patients (73%) had unequivocal recurrent lesions defined as a Rutgeerts' score >i0 at 1 year. However, for the purposes of this review question, endoscopic relapse was defined as a Rutgeerts' score ≥i2, which is reflected in the lower probabilities of relapse reported in Table 28.

Baseline rates were estimated by assuming a constant hazard rate within each time period for which data on the number of relapses were reported. This was carried out in WinBUGS in order to generate a CODA output of baseline log hazard rates that preserved correlation of estimates across time periods.

Table 28: Baseline rate and probability of relapse with no maintenance treatment following surgery for Crohn's disease

	ln(rate) (SE)	Prob (SE) per year	Prob (SE) per 2-month cycle
Endoscopic relapse			
Year 1	-0.078 (0.142)	60.3% (5.2%)	14.3% (3.7%)
Year 2	-1.603 (0.294)	18.2% (4.1%)	3.3% (1.9%)
Year 3	-1.603 (0.294)	18.2% (4.1%)	3.3% (1.9%)
Clinical relapse			
Year 1	-1.515 (0.239)	19.8% (4.2%)	3.6% (2.0%)
Year 2	-2.056 (0.344)	12.0% (3.5%)	2.1% (1.5%)
Year 3	-3.180 (0.626)	4.0% (2.1%)	0.7% (0.9%)

SE = standard error

An alternate source of baseline relapse rates was explored by pooling data from the placebo arms of the RCTs that informed the NMA. All RCTs with a placebo arm were included as there was no particular study that was considered more representative of a UK population or of UK clinical practice. However, there was evidence of heterogeneity between studies that

resulted in either non-convergence of random effects models or a poor fit to the data. As a result, data from the Rutgeerts (1990) study were used to inform the baseline rate of relapse n the economic model. The committee discussed that although it is an older study, the relapse rates reported in Rutgeerts (1990) are broadly in line with their experiences in current clinical practice.

Treatment effects for post-surgical maintenance of remission

Network meta-analysis was undertaken to estimate the relative effects of treatments for post-surgical maintenance of remission for the following outcomes: withdrawal due to adverse events, endoscopic relapse and clinical relapse. More detailed descriptions of the methods and results of the NMAs are provided in Appendix B and Appendix I respectively.

For each outcome of interest, relative effects for each treatment (d) in comparison to placebo were estimated as log hazard ratios (assuming a binomial likelihood and cloglog link function) and combined with the baseline log hazard rates (A) for each time period estimated from the Rutgeerts (1990) natural history study. The inverse cloglog transformation was used to generate absolute transition probabilities (T) per cycle for each treatment in the economic model using the following formula:

$$T[j,k] = 1 - exp\big(-exp(ln(time[j]) + A[j] + d[k])\big)$$

where

$j = time\ period\ index$

$k = treatment\ index$

$time = cycle\ length$

The baseline rate of withdrawals due to adverse events for people not receiving any post-surgical maintenance treatment was assumed to be 0. In order to estimate treatment-specific absolute probabilities of withdrawal, information for one of the active treatments (mesalazine) was incorporated into the baseline rate (A) and the log hazard ratio for withdrawal on mesalazine was then subtracted from the relative effect of each active treatment (d) . The withdrawal rate for mesalazine was estimated by pooling the mesalazine arms of all the studies that included this treatment option in the NMA. Mesalazine was selected as the baseline treatment because it was the next most frequent comparator in the network after placebo.

Given the data that were available across RCTs, it was not possible to take account of the statistical dependency between withdrawal due to adverse events and endoscopic (or clinical) relapse in the NMA and therefore each outcome was analysed independently. In the economic model, probabilities for withdrawal due to adverse events, relapse and remission cannot sum to >1 so the probabilities of experiencing disease relapse or remaining in remission were applied conditional on non-withdrawal. People withdrawing from post-surgical maintenance treatment were assumed to be in remission and transitioned to a separate health state for post-surgical remission (no maintenance) where they faced a rate of relapse associated with no treatment. The probabilities of relapse and remission were then applied to the remaining people in the post-surgical (on maintenance) health state who had not

withdrawn from treatment. Table 29 summarises the transition probabilities from the starting state post-surgical (on maintenance) in the base-case analysis using endoscopic relapse data and assuming a 3-year time horizon.

Table 29: Transition probabilities per 2-month cycle (endoscopic relapse) in the base-case analysis

Treatment	Prob withdrawal[(a)]	Prob endoscopic relapse given non-withdrawal[(a)]		Prob remission given non-withdrawal[(a)]	
		Year 1	Year 2+	Year 1	Year 2+
No treatment	0.0%	14.3%	3.3%	85.7%	96.7%
Adalimumab	0.5%	1.0%	0.2%	98.4%	99.2%
Azathioprine	2.1%	9.4%	2.1%	88.5%	95.8%
Budesonide	0.5%	13.9%	3.2%	85.7%	96.4%
Infliximab	0.9%	3.7%	0.8%	95.5%	98.3%
Mercaptopurine	0.6%	7.3%	1.6%	92.1%	97.8%
Mesalazine	0.8%	11.8%	2.7%	87.4%	96.5%
Metronidazole	2.4%	10.2%	2.3%	87.4%	95.2%
INF+MES	5.7%	2.1%	0.5%	92.3%	93.9%
MET+ADA	0.1%	4.7%	1.0%	95.2%	98.9%
MET+AZA	1.2%	5.5%	1.2%	93.4%	97.6%

(a) Excluding background risk of mortality

Treatment effects following relapse

Induction of remission with glucocorticosteroids and immunosuppressants

For people whose disease relapses following surgery, the model assumes they transition to a state of active disease and receive further treatment to induce remission as recommended elsewhere in this guideline. Probabilities for withdrawal due to adverse events and remission given non-withdrawal for first-line glucocorticosteroids and second-line azathioprine or methotrexate in combination with a glucocorticosteroid were taken from the NMA and economic model for induction of remission in the 2012 guideline (Table 30).

Table 30: Effectiveness inputs for induction of remission with first-line glucocorticosteroids and second-line azathioprine or methotrexate in combination with a glucocorticosteroid

	Prob withdrawal (SE)	Prob remission given non-withdrawal (SE)	Source
First line			
Glucocorticosteroid	13.2% (9.9%)	66.1% (6.7%)	Induction of remission NMA and economic model, 2012 guideline
Second line			
Azathioprine + glucocorticosteroid	9.8% (17.9%)	65.7% (15.1%)	Induction of remission NMA and economic model, 2012 guideline

	Prob withdrawal (SE)	Prob remission given non-withdrawal (SE)	Source
Methotrexate + glucocorticosteroid	14.9% (22.4%)	60.8% (17.4%)	Induction of remission NMA and economic model, 2012 guideline
SE = standard error			

Maintenance treatment following medically-induced remission

Following medically-induced remission, the model assumes that people will receive maintenance treatment with azathioprine or mercaptopurine as recommended in the 2012 guideline. Pooled estimates for the probability of withdrawal due to adverse events and the probability of relapse were obtained from two RCTs that were identified in the 2012 guideline (Table 31). Both of these studies compared azathioprine to placebo; in the cost-effectiveness model, the effectiveness of mercaptopurine for maintenance of medically-induced remission was assumed to be equivalent to azathioprine. For people who withdrew from azathioprine or mercaptopurine maintenance treatment following medically-induced remission, the subsequent probability of relapse was estimated from the placebo arms of the 2 trials.

Table 31: Effectiveness inputs for azathioprine maintenance treatment (following medically-induced remission)

	Prob (SE)	Source
Maintenance of medically-induced remission		
Withdrawal due to adverse events	0.5% (0.4%)	Lémann 2005, O'Donoghue 1978
Relapse	0.8% (0.6%)	
Following withdrawal from azathioprine		
Relapse	4.2% (1.0%)	Placebo arms of Lémann 2005, O'Donoghue 1978
SE = standard error		

Induction of remission with biologic therapies

If remission is not achieved with conventional treatment including glucocorticosteroids and immunosuppressive treatment, the model assumes people receive treatment with either infliximab or adalimumab as recommended in NICE technology appraisal guidance 187. Estimates of initial response to infliximab and adalimumab were obtained from the Targan 1997 and Hanauer 2006 studies respectively. People whose disease responds to biologic therapies were assumed to continue to receive a planned course of maintenance treatment for 12 months, at which point their disease would be reassessed. The probabilities of withdrawal due to adverse events and relapse during the maintenance treatment phase were obtained from the ACCENT I trial for infliximab and by pooling estimates from the CHARM and CLASSIC II trials for adalimumab (Table 32). For the downstream induction of remission pathway in the cost-effectiveness model, a combined estimate of the effectiveness of the biologic therapies was assumed. Weighted probabilities for initial response, withdrawal due to adverse events and relapse for biologic therapies were estimated by assuming 49% of people received infliximab and 51% of people received adalimumab (2016 IBD national

clinical audit of biological therapies).The probability of relapse for people following withdrawal from biologic therapies was estimated by pooling the placebo arms of all 3 trials.

Table 32: Effectiveness inputs for biologic therapies to induce and maintain remission

	Prob (SE) per 2-month cycle	Source
Initial phase - response (first cycle)		
Infliximab	91.9% (5.9%)	Targan 1997
Adalimumab	58.4% (1.9%)	Hanauer 2006 (CLASSIC I)
Withdrawal due to adverse events		
Infliximab	2.7% (0.5%)	Hanauer 2006 (ACCENT I)
Adalimumab	1.2% (0.3%)	Colombel 2007 (CHARM)
Maintenance phase - relapse		
Infliximab	18.4% (3.6%)	Hanauer 2006 (ACCENT I)
Adalimumab	13.5% (2.6%)	Colombel 2007 (CHARM), Sandborn 2007 (CLASSIC II)
Following withdrawal from infliximab or adalimumab	27.6 (1.8%)	Placebo arms of Hanauer 2006 (ACCENT I), Colombel 2007 (CHARM), Sandborn 2007 (CLASSIC II)
SE = standard error		

Health-state utilities

Health-state utilities reflecting active Crohn's disease and remission were sourced from the literature to estimate QALYs in the cost-effectiveness model. Health-state utilities were based on the same source (Stark 2010) that was used in the economic models for induction of remission and maintenance of medically-induced remission the 2012 guideline. The publication reports utilities measured in 270 people with Crohn's disease using the EuroQoL 5 dimension questionnaire (EQ-5D) and valued using the UK tariff. The utility parameters used in the model are reported in Table 33.

For the downstream induction of remission pathway in the model, it was assumed that people whose disease entered remission would do so half-way through the 2-month cycle. In people undergoing reoperation, it was assumed they would have a lower health-state utility in the immediate post-operative period before experiencing an improvement in utility associated with remission. Therefore, the utility for reoperation was calculated using a weighted average of the active disease utility (25%) and the remission state utility (75%).

Table 33: Health-state utilities used in the cost-effectiveness model

Health state	Value	Source
Active disease	0.61	Stark 2010
Remission	0.89	Stark 2010
Reoperation	0.82	Calculated (weighted assumption)

It was not possible to identify suitable disutility values in the literature to apply to people withdrawing from treatment due to adverse events. The impact of assuming a -0.05 disutility for all withdrawals due to adverse events was explored in a scenario analysis.

Costs

There were 4 categories of costs included in the model:

- **Drug costs** – acquisition costs of drugs to maintain or induce remission plus any administration costs
- **Drug monitoring costs** – healthcare costs related to preliminary checks at start of therapy or therapeutic monitoring during active treatment
- **Disease state costs** – resources associated with disease monitoring, appointments and hospital admissions in the active disease state and remission state
- **Surgery costs** – cost of reoperation

Drug costs

Drug costs were obtained from the online version of the British National Formulary (BNF) in September 2018. Where multiple preparations of a drug were available, the volume of prescriptions was extracted from the NHS Prescription Cost Analysis data (July 2018) and used to calculate a weighted cost per dose as defined in the BNF. The total cost of each drug per cycle was based on the weighted cost per dose multiplied by the frequency of administration. When dosage was based on body weight, an average assumption of 77 kg weight was used.

Infliximab and adalimumab are given at a higher frequency or dose for an initial induction period followed by an episodic or maintenance phase in people who are responding to treatment. The estimate of the cost of infliximab took into account the availability of biosimilars. National utilisation rates were sourced from the Commissioning framework for biological medicines report published by NHS England (2017), and used to calculate a weighted average cost per cycle assuming 79.9% biosimilar and 20.1% originator infliximab. In the cost-effectiveness model, infliximab and adalimumab feature as interventions in both the post-surgical maintenance of remission setting as well as the induction of remission setting. For the downstream induction of remission pathway of the model, a weighted cost per cycle for biologic therapies was used, assuming 49% of people would receive infliximab and 51% of people would receive adalimumab (2016 IBD national clinical audit of biological therapies).

The committee was aware that the patent for adalimumab was due to expire in October 2018, potentially leading to the availability of less expensive biosimilars. However, at the time of carrying out this anlaysis, information on the cost of any adalimumab biosimilar was not available. An exploratory analysis was carried out to assess the impact of reducing the cost per dose for both infliximab and adalimumab by 25%, 50% and 75%.

For other drugs used in the induction of remission pathway, the following assumptions were made:

- The cost of a course of glucocorticosteroids was based on an assumption that 90% of people would receive an 8-week tapering course of prednisolone at an initial dose of 40mg and 10% of people would receive intravenous hydrocortisone, followed by standard course of oral prednisolone.

- The cost of methotrexate assumed one outpatient appointment for the first injection of intramuscular methotrexate, and education on therapy monitoring, 10 minutes of practice nurse time for intramuscular administration of the remaining methotrexate doses and the cost of oral folic acid used to prevent toxicity.

Drug monitoring costs

The model also took into account administration and monitoring costs associated for all other treatments. This included both one-time costs of blood tests or examinations at the start of treatment as well as ongoing monitoring costs. The assumptions for these were elicited from the committee (Table 38).

Disease state costs

To estimate other healthcare costs unrelated to drugs for the management of Crohn's disease, estimates of the frequency of medical tests, appointments and hospital admissions were elicited from the committee (Table 39). These were multiplied by their respective unit costs extracted from NHS Reference Costs 2016/17 or other published sources (Table 40). Different estimates of resource use were elicited for the first year following surgery versus subsequent years. The resulting cost of one cycle in remission or relapse is reported in Table 41.

Surgery costs

The cost of reoperation was calculated as a weighted average of NHS Reference Costs 2016/17 for elective and non-elective admissions for inflammatory bowel disease adjusted for excess bed days. An assumption was made that 3% of patients who underwent reoperation would receive enteral nutrition.

Table 34: Cost of drugs for maintenance of remission

Drug	Cost per pack	Doses	Average daily dose[a]	Cost per day	Weighting (PCA)	Weighted cycle cost
Azathioprine 25 mg tablets	£1.30	28	190 mg (2.5 mg/kg)	£0.37	14.6%	£11.43
Azathioprine 50 mg tablet	£2.20	56	190 mg (2.5 mg/kg)	£0.16	85.4%	
Budesonide 3 mg CR capsules Entocort	£84.15	100	6 mg	£1.68	28.6%	£94.22
Budesonide 3 mg GR capsules (Budenofalk)	£75.05	100	6 mg	£1.50	71.4%	
Mercaptopurine 50 mg tablets	£49.15	25	100mg (1mg/kg)	£3.93	-	£238.54
Mesalazine 400 mg MR GR tablets (Asacol)	£27.45	84	2,400 mg	£1.96	29.3%	£94.75
Mesalazine 400 mg MR GR tablets (Octasa)	£16.58	90	2,400 mg	£1.11	31.1%	
Mesalazine 800 mg MR GR (Asacol)	£54.90	84	2,400 mg	£1.96	18.0%	
Mesalazine 800 mg MR GR (Octasa)	£80.75	180	2,400 mg	£1.35	21.6%	
Metronidazole 400 mg tablets[b]	£4.30	21	1,200 mg (20mg/kg)	£0.61	-	£37.27
Sulfasalazine 500 mg tablets	£7.83	112	3 g	£0.42	29.2%	£26.83
Sulfasalazine 500 mg GR tablets	£8.43	112	3 g	£0.45	70.8%	
PCA = Prescription Cost Analysis data from NHS Business Services Authority						

(a) Budesonide, metronidazole and sulfasalazine are not licenced for maintenance of remission of Crohn's disease. The maximum dose used in the clinilcal trials was used to calculate costs. The doses of azathioprine, mercaptopurine and mesalazine were inconsistent in clinical trials, maximum dose recommended in BNF was used.
(b) Metronidazole given for a maximum of 3 months.

Table 35: Cost of biologic therapies for maintenance and induction of remission

Drug	Cost per pack	Doses	Dose	Cost per cycle
Adalimumab 40mg/0.8ml (Humira)	£704.28	2	160mg - initially 80mg – after 2 weeks 40mg – every 2 weeks	Initial cycle: £2,817.12 Subsequent cycles: £1,408.56
Adalimumab 20mg/0.2 ml (Humira)	£352.14	2		
Infliximab 100mg/vial (Remicade)	£419.62	1	5mg/kg initially, repeated at 2 and 4 weeks 5mg/kg every 4 weeks thereafter	Initial cycle: £4,634[a] Subsequent cycles: £1,545[a]
Infliximab biosimilar 100mg/vial	£377.66	1		

(a) Weighted average assuming 79.9% biosimilar and 20.1% originator infliximab (NHS England 2017 Commissioning framework for biological medicines report)

Table 36: Cost of drugs for induction of remission

Drug	Cost per pack	Doses	Average daily dose	Cost per day	Weighting (PCA)	Weighted cycle cost
Glucocorticosteroids						
Prednisolone 5 mg tablets	£0.76	28	40 mg tapered	£0.22	84.0%	£6.71[(a)]
Prednisolone 5 mg GR tablets	£1.08	28	40 mg taprered	£0.31	6.7%	
Hydrocortisone 100 mg/1ml for injection	£8.33	5	300 mg	£5.00	32.3%	
Hydrocortisone 100 mg powder for injection	£9.71	10	300 mg	£2.91	43.6%	
Hydrocortisone 100 mg powder and solvent for injection	£1.16	1	300 mg	£3.48	24.1%	
Immunosuppressants						
Azathioprine 25 mg tablets	£1.30	28	190 mg (2.5 mg/kg)	£0.37	14.6%	£11.43
Azathioprine 50 mg tablet	£2.20	56	190 mg (2.5 mg/kg)	£0.16	85.4%	
Drug	**Cost per pack**	**Doses**	**Average weekly dose**	**Cost per week**	**Weighting (PCA)**	**Cycle cost**
Immunosuppressants						
Methotrexate 25 mg/1 ml pre-filled syringes (Zlatal)	£16.64	1	25 mg	£16.64	-	£131.12
Folic acid 5mg tablets	£0.66	28	5 mg	£0.02	-	£0.19
PCA = Prescription Cost Analysis data from NHS Business Services Authority						

(a) Assumes 90% of people receive prednisolone and 10% receive intravenous hydrocortisone

Table 37: Cost of enteral nutrition and supplements

Drug	Cost per pack	Doses	Average daily dose	Cost per day	Weighting (PCA)	Weighted cycle cost
Ensure liquid 259 ml (several flavours)	£2.31	1	3	£6.93	76.1%	£443.82[(a)]
Ensure plus Crème 500gr	£7.72	1	3	£23.16	2.9%	
Fresubin 2Kcal drink	£2.12	1	3	£6.36	21.0%	
PCA = Prescription Cost Analysis data from NHS Business Services Authority						

(a) Cost applied to 3% of patients in the surgical state

Table 38: Assumptions about testing and monitoring requirements for each treatment

	At treatment initiation (one-time)	Annual monitoring	
	% patients	Frequency	% patients
Adalimumab and infliximab			
Test for latent TB (interferon gamma test)	100%	0	-
Chest X-ray	100%	0	-
Virology tests for Hep B, Hep C and chickenpox	100%	0	-
Dermatology appointment	0%	1	100%
Level of biologic in blood serum	0%	3	100%
Infusion cost (infliximab)	-	8	100%
Azathioprine and mercaptopurine			
Liver function tests	100%	4	100%
Full blood count	100%	4	100%
Virology test for Hep B, Hep C and chickenpox	100%	0	-
TPMT test (enzyme)	10%	0	-
6-TG, 6-MMP		2	100%
Glucocorticosteroids			
DEXA scan	1%	1	20%
Liver function tests, renal function	0%	1	100%
Metronidazole			
Liver function tests, renal function	100%	3	100%
Methotrexate			
Pregnancy test	50%	-	-
Liver function tests	-	3	100%
Full blood count	-	3	100%
Mesalazine			
Liver function tests, renal function	100%	2	100%
Sulfazalazine			
Full blood count	100%	2	100%
Liver function tests, renal function	100%	2	100%

DEXA = dual-energy X-ray absorptiometry; 6-MMP = 6-methylmercaptopurine; TB = tuberculosis; 6-TG = 6-thioguanine; TPMT = thiopurine methyltransferase

Table 39: Estimates of other healthcare resource use by disease state

	Remission			Active disease	
	% patients	Annual rate		% patients	Annual rate
		Year 1	≥Year 2		
Appointments and admissions					
Gastroenterology	100%	2	1	100%	4
Surgical	5%	-	-	28%	1
Rheumatology	5%	1	1	16%	1
Dermatology	1%	1	1	12%	1
General practitioner	100%	2	2	100%	2.6
IBD nurse	100%	2	1	100%	7.8
IBD nurse phone	100%	2	2	100%	15.6
Stoma nurse	12%	4	1	12%	2
Dietitian	20%	2	1	20%	2
Emergency department visit	-	-	-	16%	1
Inpatient admission	-	-	-	14%	1
Clinical biochemistry					
Haematology (full blood count)	100%	1	1	100%	6
Biochemistry (liver function, renal function)	100%	1	1	100%	6
Faecal calprotectin	100%	1	1	100%	4
Plebotomy	100%	1	1	100%	6
Endoscopy					
Oesophago-gastroduodenoscopy	25%	1	-	25%	1
Sigmoidoscopy	-	1	-	15%	1
Colonoscopy	100%	1	0.1	75%	1
Capsule endoscopy	-	-	-	5%	1
Radiology and examinations					
Plain X-ray	14%	1	-	20%	1
Barium enema	-	-	-	1%	1
Barium follow through	-	-	-	1%	1
USS abdomen	-	-	-	36%	1
CT abdomen/pelvis	-	-	-	30%	1
MRI abdomen/pelvis	-	-	-	50%	1
White blood cell scan	-	-	-	1%	1
Fistulogram	-	-	-	2%	1

Table 40: Unit costs used in the economic model

Resource	Cost	Source
Appointments and admissions		
Gastroenterology consultant led [301]	£137	NHS reference cost 2016/2017
Colorectal surgery consultant led [301]	£108	NHS reference cost 2016/2017
Rheumatologist [WF01A]	£139	NHS reference cost 2016/2017
Dermatologist [WF01A]	£78	NHS reference cost 2016/2017
General practitioner	£38	PSSRU 2017
IBD nurse [WF01A, 301]	£107	NHS reference cost 2016/2017
IBD nurse phone [WF01C, 301]	£113	NHS reference cost 2016/2017
Specialist stoma nurse [N24AF]	£51	NHS reference cost 2016/2017
Dietitian [AHP, A03]	£85	NHS reference cost 2016/2017
Emergency department visit [WF01B - 180]	£148	NHS reference cost 2016/2017
Inpatient admission [FD02A-H]	£2,378	NHS reference cost 2016/2017
Infusion of infliximab [Gastroenterology, non-consultant led, 301]	£107	NHS reference cost 2016/2017
Admission for infusion of hydrocortisone [FD02E-H]	£1,957	NHS reference cost 2016/2017
First methotrexate injection and education [Gastroenterology, non-consultant led, 301]	£107	NHS reference cost 2016/2017
Intramuscular injection of methotrexate [Practice nurse, hourly rate][(a)]	£36	PSSRU 2017
Clinical biochemistry and microbiology		
Full blood count	£3	NHS reference cost 2016/2017
Biochemistry (liver or renal function)	£1	NHS reference cost 2016/2017
Phlebotomy	£3	NHS reference cost 2016/2017
Faecal calprotectin	£30	Sandwell and West Birmingham Hospitals
Test for latent TB (interferon gamma test)	£8	NHS reference cost 2016/2017
Virology tests for Hep B, Hep C and Chickenpox	£8	NHS reference cost 2016/2017
TPMT test (enzyme)	£24	Sandwell and West Birmingham Hospitals 2018
Thioguanine nucleotides (6-TGN & 6-MMPN)	£32	Sandwell and West Birmingham Hospitals 2018
Infliximab level	£30	Sandwell and West Birmingham Hospitals 2018
Endoscopy		
Capsule endoscopy [FE50A]	£512	NHS reference cost 2016/2017
OGD [FE22Z]	£307	NHS reference cost 2016/2017
Sigmoidoscopy [FE35Z]	£175	NHS reference cost 2016/2017
Colonoscopy [FE31Z]	£353	NHS reference cost 2016/2017
Radiology and examinations		
Plain X-ray	£25	Stockport NHS Foundation 2014
Barium enema [IMAGOP,RD30Z, outpatient]	£126	NHS reference cost 2016/2017

Resource	Cost	Source
Barium follow through [IMAGOP, RD32Z, outpatient]	£169	NHS reference cost 2016/2017
USS abdomen [IMAGOP, RD42Z, outpatient]	£65	NHS reference cost 2016/2017
CT abdomen/pelvis [IMAGOP, RD24Z, outpatient]	£112	NHS reference cost 2016/2017
MRI abdomen s bowel [IMAGOP, RD04Z, outpatient]	£158	NHS reference cost 2016/2017
White blood cell scan [IMAGOP, RN13Z, outpatient]	£183	NHS reference cost 2016/2017
Fistulogram [IMAGOP, RD32Z, outpatient]	£169	NHS reference cost 2016/2017
DEXA scan	£83	NHS reference cost 2016/2017

(a) It was assumed that an intramuscular injection of methotrexate would require 10 minutes of a practice nurse time.

Table 41: Other disease state costs

Health state	Cost per cycle
Remission (year 1)	£221
Remission (after year 1)	£108
Active disease	£716

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken to take into account parameter uncertainty in the model. To account for uncertainty in the estimates of relative effects of treatments for post-surgical maintenance of remission from the NMAs, CODA outputs containing 10,000 iterations for each outcome were produced in WinBUGS after running 50,000 simulations and thinning the data by 5 to reduce autocorrelation. For input parameters sourced from the literature, summary statistics characterising each parameter were extracted where possible or calculated according to the type of data. Beta distributions were used for parameters denoting probabilities and for health state utilities, as these used values between 0 and 1. The source of health-state utilities from Stark 2010 did not report any negative values. Gamma distributions were used for cost parameters, given they are positively skewed and non-negative. Probability distributions were assigned to most input variables (Table 42) with the exception of drug costs and the frequencies of drug monitoring and background resource use that were elicited from the committee.

Monte Carlo simulation was used to randomly sample 1,000 times from the CODAs and available distributions. Incremental cost-effectiveness results are presented as the mean of all probabilistic interations along with the probability that each strategy is cost effective at a threshold of £20,000/QALY.

Table 42: Summary of assumptions for parameter uncertainty used in probabilistic sensitivity analysis

Parameter	Point estimate	Distribution	Parameters	Source
Baseline rate ln(rate)				

Parameter	Point estimate	Distribution	Parameters	Source
Endoscopic relapse (Rutgeerts≥i2)				
Year 0 to 1	-0.078	CODA	-	Rutgeerts 1990
Year 1 to 3	-1.603	CODA	-	Rutgeerts 1990
Clinical relapse				
Year 0 to 1	-1.511	CODA	-	Rutgeerts 1990
Year 1 to 2	-2.053	CODA	-	Rutgeerts 1990
Year 2 to 3	-3.189	CODA	-	Rutgeerts 1990
Withdrawal due to adverse events				
Mesalazine	-3.193	Normal	μ=-3.193 σ=1.370	NMA
Treatment effects				
Post-surgical maintenance of remission				
Endoscopic relapse ln(HR)				
Adalimumab	-2.742	CODA	-	NMA
Azathioprine	-0.453	CODA	-	NMA
Budesonide	-0.038	CODA	-	NMA
Infliximab	-1.414	CODA	-	NMA
Mercaptopurine	-0.709	CODA	-	NMA
Mesalazine	-0.205	CODA	-	NMA
Metronidazole	-0.356	CODA	-	NMA
INF+MES	-1.996	CODA	-	NMA
MET+ADA	-1.461	CODA	-	NMA
MET+AZA	-1.006	CODA	-	NMA
Clinical relapse ln(HR)				
Adalimumab	-2.356	CODA	-	NMA
Azathioprine	-0.320	CODA	-	NMA
Budesonide	-0.100	CODA	-	NMA
Infliximab	-0.573	CODA	-	NMA
Mercaptopurine	-0.346	CODA	-	NMA
Mesalazine	-0.262	CODA	-	NMA
Metronidazole	-0.478	CODA	-	NMA
INF+MES	-0.518	CODA	-	NMA
MET+ADA	-2.139	CODA	-	NMA
MET+AZA	-1.037	CODA	-	NMA
Sulfasalazine	-0.423	CODA	-	NMA
Withdrawal due to adverse events ln(HR)				
Adalimumab	0.170	CODA	-	NMA
Azathioprine	1.535	CODA	-	NMA
Budesonide	-0.013	CODA	-	NMA
Infliximab	0.621	CODA	-	NMA
Mercaptopurine	0.182	CODA	-	NMA

Parameter	Point estimate	Distribution	Parameters	Source
Mesalazine	0.557	CODA	-	NMA
Metronidazole	1.681	CODA	-	NMA
INF+MES	2.538	CODA	-	NMA
MET+ADA	-2.062	CODA	-	NMA
MET+AZA	0.919	CODA	-	NMA
Sulfasalazine *(same as mesalazine)*	0.557	CODA	-	NMA
Induction of remission				
Clinical remission (probability)				
First-line glucocorticosteroid	0.661	CODA	-	Induction of remission NMA and economic model, 2012 guideline
Second-line azathioprine + glucocorticosteroid	0.657	CODA	-	
Second-line methotrexate + glucocorticosteroid	0.608	CODA	-	
Infliximab	0.919	CODA	-	Targan 1997
Adalimumab	0.585	CODA	-	Hanauer 2006
Withdrawal due to adverse events (probability)				
First-line glucocorticosteroid	0.132	CODA	-	Induction of remission NMA and economic model, 2012 guideline
Second-line azathioprine + glucocorticosteroid	0.098	CODA	-	
Second-line methotrexate + glucocorticosteroid	0.149	CODA	-	
Proportion on INF vs ADA	48.8%	Beta	α=845 β=888	UK IBD Registry 2016
Proportion of individuals on biosimilar infliximab	79.7%	Beta	α=86.076 β=21.924	NHS England Commissioning framework for biological medicines report 2017
Maintenance of medically-induced remission				
Clinical relapse on maintenance (probability)				
Azathioprine	0.008	Beta	α=1.918 β=227.106	Lémann 2005, O'Donoghue 1978
Infliximab	0.184	CODA	-	Hanauer 2006
Adalimumab	0.135	CODA	-	Colombel 2007, Sandborn 2007
Withdrawal due to adverse events (probability)				
Azathioprine	0.005	Beta	α=2.079 β=392.436	Lémann 2005, O'Donoghue 1978
Infliximab	0.027	Beta	α=28.858 β=1049.046	Hanauer 2006

Parameter	Point estimate	Distribution	Parameters	Source
Adalimumab	0.012	Beta	α=17.970 β=1493.868	Colombel 2007
Clinical relapse no maintenance (probability)				
Azathioprine	0.042	Beta	α=15.949 β=360.952	Lémann 2005, O'Donoghue 1978
Infliximab + Adalimumab	0.276	Beta	α=179.526 β=471.478	Hanauer 2006, Colombel 2007, Sandborn 2007
Costs				
Clinical biochemistry and microbiology (directly accessed)				
Haematology [DAPS05], full blood count	£3	Gamma	α=957.542 β=0.003	National Ref Cost 2016/17
Clinical biochemistry (liver or renal function) [DAPS04]	£1	Gamma	α=933.156 β=0.001	National Ref Cost 2016/17
Phlebotomy [DAPS08]	£3	Gamma	α=134.226 β=0.023	National Ref Cost 2016/17
Faecal calprotectin	£30	-	-	Sandwell and West Birmingham Trust
Test for latent tuberculosis (interferon gamma test) [microbiology, DAPS07]	£8	Gamma	α=695.889 β=0.011	National Ref Cost 2016/17
Virology tests for Hep B, Hep C and chickenpox [microbiology, DAPS07]	£8	Gamma	α=695.889 β=0.011	National Ref Cost 2016/17
TPMT test (enzyme)	£24	-	-	Sandwell and West Birmingham Trust
Thioguanine nucleotides (6-TGN & 6-MMPN)	£32	-	-	Sandwell and West Birmingham Trust
Infliximab level	£30	-	-	Sandwell and West Birmingham Trust
Endoscopy (gastroenterology, outpatient)				
Capsule endoscopy [FE50A]	£516	Gamma	α=504.726 β=0.609	National Ref Cost 2016/17
Oesophago-gastroduodenoscopy [FE22Z]	£307	Gamma	α=954.591 β=0.322	National Ref Cost 2016/17
Sigmoidoscopy [FE35Z]	£175	Gamma	α=70.795 β=2.475	National Ref Cost 2016/17
Colonoscopy [FE31Z]	£353	Gamma	α=135809634.077 β=0.000	National Ref Cost 2016/17

Parameter	Point estimate	Distribution	Parameters	Source
Radiology and examinations (outpatient)				
Plain X-ray	£25	-	-	FOI Request (23023) Stockport NHS Trust 2014
Barium enema [RD30Z]	£126	Gamma	α=16105.803 β=0.008	National Ref Cost 2016/17
Barium follow through [RD32Z]	£169	Gamma	α=3889.859 β=0.043	National Ref Cost 2016/17
Ultrasound abdomen [RD42Z]	£65	Gamma	α=12507.015 β=0.005	National Ref Cost 2016/17
CT abdomen/pelvis [RD24Z]	£112	Gamma	α=40270.694 β=0.003	National Ref Cost 2016/17
MRI abdomen s bowel [RD04Z]	£158	Gamma	α=18868.682 β=0.008	National Ref Cost 2016/17
White blood cell scan [RN13Z]	£183	Gamma	α=1481.966 β=0.124	National Ref Cost 2016/17
Fistulogram [RD32Z]	£169	Gamma	α=3889.859 β=0.043	National Ref Cost 2016/17
DEXA scan [RD50Z]	£83	Gamma	α=15540.607 β=0.005	National Ref Cost 2016/17
Appointments, admissions and surgery				
Gastroenterology consultant led [301]	£141	Gamma	α=1746.500 β=0.081	National Ref Cost 2016/17
Gastroenterology non-consultant led [301]	£107	Gamma	α=585.645 β=0.182	National Ref Cost 2016/17
Colorectal surgery consultant led [104]	£112	Gamma	α=450.508 β=0.249	National Ref Cost 2016/17
Colorectal surgery non-consultant led [104]	£89	Gamma	α=224.393 β=0.397	National Ref Cost 2016/17
Rheumatologist [WF01A]	£139	Gamma	α=1019.732 β=0.136	National Ref Cost 2016/17
Dermatologist [WF01A]	£101	Gamma	α=456.861 β=0.171	National Ref Cost 2016/17
General practitioner	£38	-	-	PSSRU 2017
IBD nurse [WF01A, 301]	£107	Gamma	α=585.645 β=0.182	National Ref Cost 2016/17
IBD nurse phone [WF01C, 301]	£113	Gamma	α=723.069 β=0.156	National Ref Cost 2016/17
Specialist stoma nurse [N24AF]	£51	Gamma	α=170.298 β=0.300	National Ref Cost 2016/17
Dietitian [AHP, A03]	£85	Gamma	α=440.794 β=0.192	National Ref Cost 2016/17

Parameter	Point estimate	Distribution	Parameters	Source
Emergency department visit [WF01B - 180]	£148	Gamma	α=324.711 β=0.457	National Ref Cost 2016/17
Cost inpatient admissions (elective)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£9,009	Gamma	α = 72.160 β = 124.849	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£4,848	Gamma	α = 152.626 β = 31.761	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£4,529	Gamma	α = 94.620 β = 47.861	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£3,393	Gamma	α = 1672.459 β = 2.029	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£2,960	Gamma	α = 266.054 β = 11.125	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£1,700	Gamma	α = 300.944 β = 5.650	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£1,290	Gamma	α = 743.071 β = 1.736	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£828	Gamma	α = 508.533 β = 1.627	NHS Ref Costs 2016/2017
Cost inpatient admissions (elective excess bed-days)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£435	Gamma	α = 4.896 β = 88.793	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£409	-	-	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£269	-	-	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£434	Gamma	α = 34.576 β = 12.552	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£379	Gamma	α = 63.315 β = 5.983	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£371	Gamma	α = 1099.660 β = 0.337	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£309	Gamma	α = 483.196 β = 0.640	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£384	Gamma	α = 260.178 β = 1.476	NHS Ref Costs 2016/2017
Cost inpatient admissions (non-elective)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£8,300	Gamma	α = 1252.396 β = 6.627	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£5,000	Gamma	α = 774.982 β = 6.452	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£5,050	Gamma	α = 5151.508 β = 0.980	NHS Ref Costs 2016/2017

Parameter	Point estimate	Distribution	Parameters	Source
IBD Single Intervention, CC Score 0-3 [FD02D]	£2,820	Gamma	α = 12501.295 β = 0.226	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£2,641	Gamma	α = 15831.327 β = 0.167	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£2,134	Gamma	α = 15224.861 β = 0.140	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£1,806	Gamma	α = 31459.911 β = 0.057	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£1,648	Gamma	α = 28362.720 β = 0.058	NHS Ref Costs 2016/2017
Cost inpatient admissions (non-elective excess bed-days)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£353	Gamma	α = 261.341 β = 1.352	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£396	Gamma	α = 196.123 β = 2.022	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£321	Gamma	α = 190.149 β = 1.689	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£329	Gamma	α = 1033.307 β = 0.318	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£304	Gamma	α = 1545.016 β = 0.197	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£294	Gamma	α = 2571.506 β = 0.114	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£294	Gamma	α = 3172.810 β = 0.093	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£299	Gamma	α = 2813.486 β = 0.106	NHS Ref Costs 2016/2017
Health-state utilities				
Active disease	0.61	Beta	α=1.116 β=0.713	Stark 2010
Remission	0.89	Beta	α=4.266 β=0.527	Stark 2010

Scenario analyses

A number of scenarios were conducted to explore the impact of key assumptions on model results.

- **Scenario 1: Clinical relapse as the main outcome**
  The committee prioritised endoscopic relapse as the main outcome of interest in the economic model. An NMA was also conducted to analyse the outcome clinical relapse, which allowed the addition of one other comparator (sulfasalazine) to the decision space. In this scenario analysis, data on clinical relapse were used in place of endoscopic relapse for both the baseline rate and relative treatment effects.

- **Scenario 2: Time horizon extended to 10 years and lifetime**
  The committee felt that the base case cost-effectiveness analysis should be limited to 3 years because this reflected the duration of follow-up from RCTs used to estimate treatment effects. A scenario analysis was undertaken to explore the effect of extending the time horizon assuming the baseline rate of relapse at 3 years and relative treatment effects remained constant.

- **Scenario 3: Methotrexate as second-line treatment for induction of remission**
  For people whose disease relapsed while receiving azathioprine or mercaptopurine as treatment for post-surgical maintenance of remission, it is unlikely that the same drug would be used again as second-line treatment to induce remission. A scenario analysis was run assuming that these people would receive methotrexate instead.

- **Scenario 4: A proportion of patients withdrawing due to adverse events while receiving maintenance treatment transition immediately to active disease**
  During data extraction, it was noticed that disease status was frequently unknown in people withdrawing due to adverse events. The base case cost-effectiveness analysis assumes that all people who withdraw from maintenance treatment (post-surgical or following medically-induced remission) are initially still in remission. A scenario analysis was run assuming that 50% of people withdrawaing from maintenance treatment due to adverse events immediately relapse, meaning that there will be a more rapid decline in their health status to active disease.

- **Scenario 5: Apply a disutility for withdrawals due to adverse events**
  It was not possible to capture reliable comparative data for specific adverse events or to identify suitable disutility values in the literature. A scenario analysis was conducted assuming that all people who withdraw from maintenance treatment due to adverse events experience a disutility of -0.05 for the remainder of the cycle.

- **Scenario 6: Continuation of biologic therapy following medically-induced remission beyond 12 months**
  The base case analysis assumes that people whose disease responds to infliximab or adalimumab for the induction of remission will continue to receive a 12-month course of treatment. A scenario analysis was run assuming that biologic therapy would continue beyond 12 months for as long as the person's disease remains in remission.

- **Scenario 7a: No azathioprine**
  The committee estimated that approximately 10-20% of adults cannot tolerate azathioprine. In this scenario, strategies using azathioprine alone or in combination with another drug to maintain remission after surgery were removed from the decision space. In addition, for patients whose disease relapsed, it was assumed they would receive methotrexate instead of azathioprine (in combination with a

glucocorticosteroid) as second-line treatment for induction of remission and mercaptopurine instead of azathioprine to maintain medically-induced remission.

- **Scenario 7b: No azathioprine and no metronidazole**
  Intolerance to metronidazole is also a concern in clinical practice. In this scenario, all strategies containing either azathioprine and/or metronidazole were removed.

- **Scenario 7c: No metronidazole**
  Not all people who are intolerant to metronidazole will be intolerant to azathioprine. This scenario excludes strategies containing metronidazole but retains azathioprine.

- **Scenario 7d: No azathioprine, no metronidazole and no mesalazine**
  There was some uncertainty about the clinical benefit of mesalazine for maintaining endoscopic remission in the NMA. An additional scenario was run to estimate ICERs removing azathioprine, metronidazole and mesalazine from the decision space.

Results

Base-case analysis

Table 43 shows the results of the cost-effectiveness model in terms of the proportion of time spent by the cohort in active disease versus remission as well as the proportion undergoing reoperation for each of the treatment strategies for post-surgical maintenance of remission. Adalimumab is the most effective treatment as it is associated with the highest proportion of time spent in remission and the lowest reoperation rate over the 3-year time horizon.

Table 43: Proportion of time in remission versus active disease and reoperation rate in the base-case analysis: endoscopic relapse, 3-year time horizon

Strategy	% time spent in remission	% time spent in active disease	% reoperation
Adalimumab	98.5%	1.2%	0.2%
Infliximab	96.3%	3.1%	0.6%
MET+ADA[(a)]	96.1%	3.2%	0.7%
MET+AZA[(a)]	95.0%	4.2%	0.9%
INF+MES	94.4%	4.7%	0.9%
Mercaptopurine	94.2%	4.8%	1.0%
Azathioprine	92.6%	6.1%	1.3%
Metronidazole[(a)]	92.2%	6.4%	1.3%
Mesalazine	92.1%	6.5%	1.4%
Budesonide	91.5%	7.1%	1.5%
No treatment	91.4%	7.1%	1.5%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

The deterministic results of the base-case endoscopic relapse analysis are presented in Table 44. The combination of metronidazole (for 3 months) and azathioprine (MET+AZA) was the least costly option and produced more QALYs than all other strategies except adalimumab. Adalimumab produced the highest total QALYs but at an incremental cost of approximately £23,000 in comparison to MET+AZA, yielding an incremental cost-effectiveness ratio (ICER) of £922,416/QALY. The probabilistic results of 1,000 iterations for this scenario are similar (Table 45), showing that at a threshold value of £20,000/QALY, there is a high degree of certainty (92.8%) that the combination MET+AZA is the most cost-effective treatment strategy for post-surgical maintenance of remission. This high degree of certainty is maintained over a range of threshold values as shown in the cost-effectiveness acceptability curve (CEAC) for the base-case endoscopic relapse analysis in Figure 97.

Table 44: Deterministic cost-effectiveness results for the base-case analysis: endoscopic relapse, 3-year time horizon

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£5,504	2.674			
Azathioprine	£6,684	2.658	£1,180	-0.016	dominated
Metronidazole[(a)]	£6,726	2.655	£1,222	-0.019	dominated
No treatment	£7,096	2.649	£1,591	-0.025	dominated
Mesalazine	£7,611	2.654	£2,107	-0.020	dominated
Budesonide	£7,984	2.649	£2,479	-0.025	dominated
Mercaptopurine	£8,595	2.669	£3,090	-0.005	dominated
MET+ADA[(a)]	£26,345	2.682	£20,840	0.008	ext. dom.
INF+MES	£27,456	2.670	£21,951	-0.004	dominated
Adalimumab	£28,465	2.699	£22,960	0.025	£922,416
Infliximab	£31,357	2.683	£2,892	-0.016	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Table 45: Mean probabilistic cost-effectiveness results for the base-case analysis: endoscopic relapse, 3-year time horizon

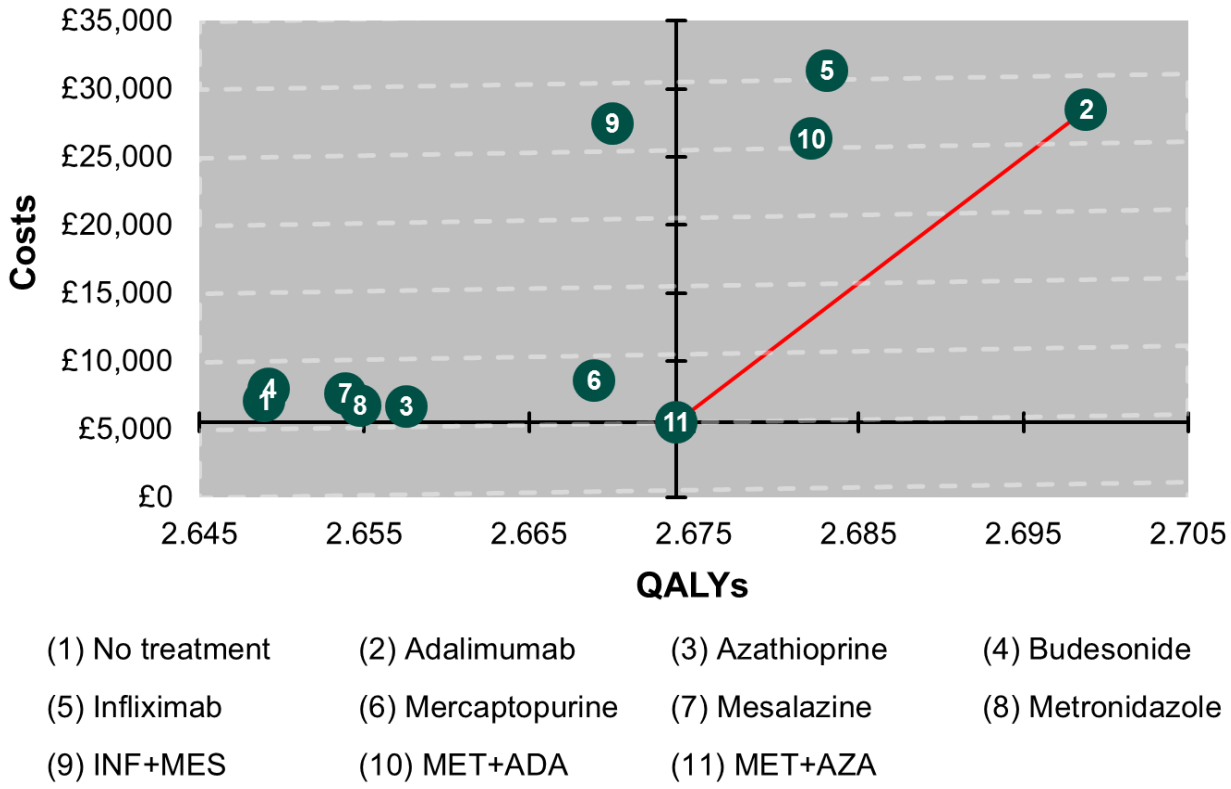
	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£5,592	2.655				92.8%
Azathioprine	£6,731	2.639	£1,139	-0.015	dominated	2.5%
Metronidazole[(a)]	£6,786	2.636	£1,194	-0.018	dominated	2.5%
No treatment	£7,135	2.631	£1,543	-0.024	dominated	1.0%
Mesalazine	£7,651	2.636	£2,059	-0.019	dominated	0.2%
Budesonide	£8,026	2.631	£2,433	-0.024	dominated	1.0%
Mercaptopurine	£8,626	2.651	£3,034	-0.004	dominated	0.0%
MET+ADA[(a)]	£25,830	2.660	£20,237	0.006	ext. dom.	0.0%
INF+MES	£27,190	2.651	£21,598	-0.004	dominated	0.0%
Adalimumab	£28,274	2.680	£22,682	0.025	£901,306	0.0%

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
Infliximab	£31,242	2.665	£2,968	-0.015	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Figure 96: Cost-effectiveness plane for the base-case analysis: endoscopic relapse, 3-year time horizon (mean probabilistic results)

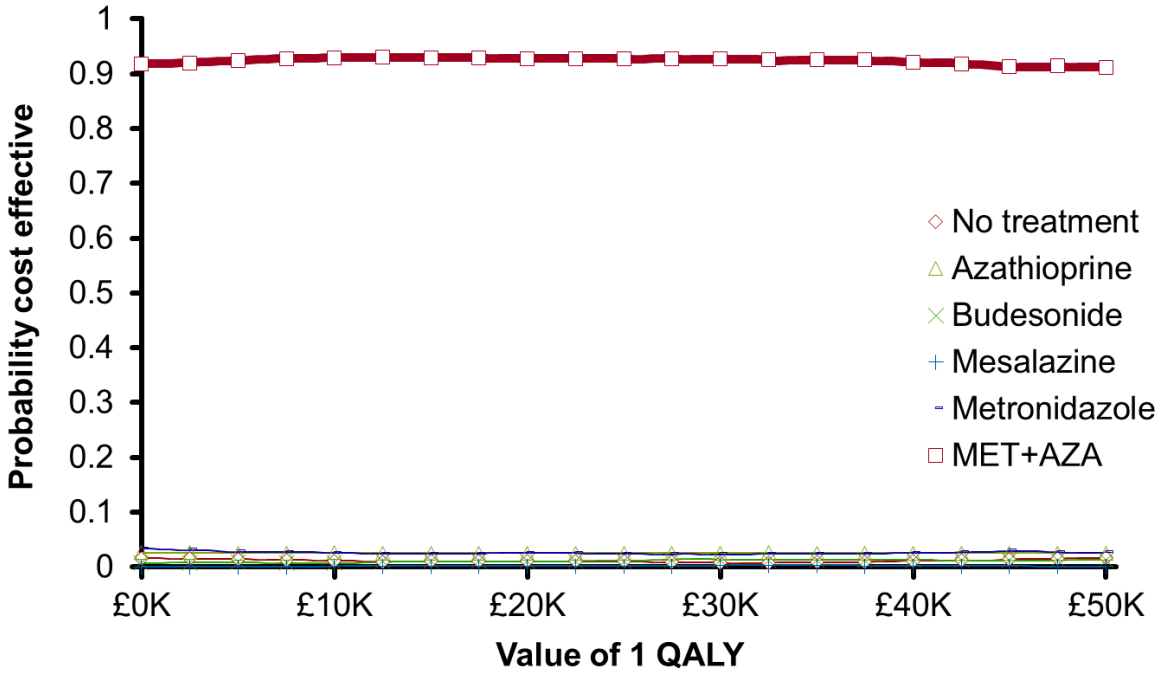


(1) No treatment (2) Adalimumab (3) Azathioprine (4) Budesonide

(5) Infliximab (6) Mercaptopurine (7) Mesalazine (8) Metronidazole

(9) INF+MES (10) MET+ADA (11) MET+AZA

Figure 97: Cost-effectiveness acceptability curve for the base-case anlaysis: endoscopic relapse, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

Scenario analyses

Scenario 1: Clinical relapse as the main outcome

Table 46 **Error! Reference source not found.**shows the deterministic results using the baseline and relative effectiveness data for clinical relapse assuming a 3-year time-horizon. The baseline rate of clinical relapse is lower than endoscopic relapse and therefore total QALYs have increased slightly for all strategies including no treatment. The ranking of strategies is similar to the endoscopic base-case analysis with MET+AZA dominating all other strategies with the exception of the combination of MET+ADA. The combination of MET+ADA generated the most QALYs but the ICER was well in excess of £20,000/QALY. Table 47 shows the mean probabilistic results of 1,000 iterations with MET+AZA having a 70.5% probability of being cost effective. The CEAC is presented in Figure 98.

Table 46: Deterministic cost-effectiveness results for scenario 1: clinical relapse, 3-year time horizon

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£3,974	2.697			
Metronidazole[(a)]	£4,371	2.689	£397	-0.008	dominated
No treatment	£4,470	2.684	£496	-0.013	dominated
Sulfasalazine	£4,511	2.690	£536	-0.006	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Azathioprine	£4,660	2.687	£686	-0.010	dominated
Mesalazine	£5,631	2.688	£1,657	-0.009	dominated
Budesonide	£5,824	2.685	£1,850	-0.011	dominated
Mercaptopurine	£7,885	2.690	£3,911	-0.007	dominated
INF+MES	£26,162	2.686	£22,188	-0.011	dominated
Adalimumab	£28,851	2.705	£24,877	0.008	ext. dom.
MET+ADA[(a)]	£29,794	2.705	£25,820	0.009	£2,960,186
Infliximab	£32,344	2.692	£2,549	-0.013	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

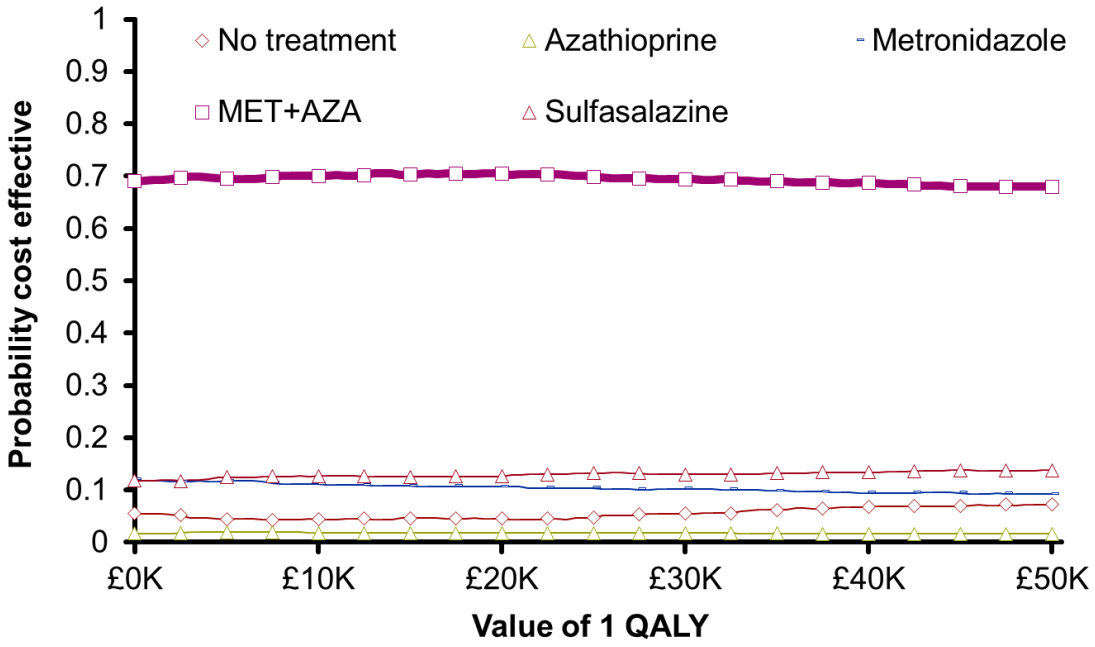
Table 47: Mean probabilistic cost-effectiveness results for scenario 1: clinical relapse, 3-year time horizon

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£4,123	2.699				70.5%
Metronidazole[(a)]	£4,485	2.691	£362	-0.007	dominated	10.6%
No treatment	£4,554	2.687	£431	-0.012	dominated	4.5%
Sulfasalazine	£4,601	2.694	£478	-0.005	dominated	12.6%
Azathioprine	£4,765	2.690	£642	-0.009	dominated	1.8%
Mesalazine	£5,700	2.691	£1,577	-0.008	dominated	0.0%
Budesonide	£5,946	2.688	£1,823	-0.011	dominated	0.0%
Mercaptopurine	£7,946	2.692	£3,823	-0.007	dominated	0.0%
INF+MES	£25,821	2.687	£21,698	-0.012	dominated	0.0%
Adalimumab	£28,774	2.709	£24,651	0.010	£2,406,637	0.0%
MET+ADA[(a)]	£29,607	2.709	£832	0.000	dominated	0.0%
Infliximab	£32,118	2.695	£3,344	-0.014	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Figure 98: Cost-effectiveness acceptability for scenario 1: clinical relapse, 3-year time horizon



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 2: Time horizon extended to 10 years and lifetime

The time horizon for the base-case endoscopic relapse analysis was expanded to 10 years and to a lifetime period. The deterministic and probabilistic results for the 10-year time horizon are presented in Table 48 and Table 49. The deterministic and probabilistic results for the lifetime horizon are presented in Table 50 and Table 51. The ranking of strategies is identical to the base-case analysis. MET+AZA retains the highest probability of being the optimal strategy in the 10-year time horizon analysis (96.4%) and in the lifetime time horizon analysis (97.2%). In comparison to the base-case results, the ICER for adalimumab versus MET+AZA has increased to >£1 million/QALY while all other strategies remain dominated. The probabilistic results for these scenarios are presented in Figure 99 and Figure 100.

Table 48: Deterministic cost-effectiveness results for scenario 2: 10-year time horizon

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£15,327	7.630			
No treatment	£17,861	7.607	£2,534	-0.024	dominated
Metronidazole[(a)]	£17,896	7.607	£2,570	-0.023	dominated
Azathioprine	£18,031	7.610	£2,705	-0.020	dominated
Mesalazine	£18,932	7.610	£3,605	-0.021	dominated
Budesonide	£19,629	7.606	£4,302	-0.025	dominated
Mercaptopurine	£21,074	7.627	£5,747	-0.003	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
INF+MES	£46,625	7.614	£31,298	-0.016	dominated
MET+ADA[(a)]	£60,657	7.651	£45,331	0.020	ext. dom.
Infliximab	£66,807	7.645	£51,481	0.014	dominated
Adalimumab	£69,837	7.675	£54,510	0.044	£1,235,245

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Table 49: Mean probabilistic cost-effectiveness results for scenario 2: 10-year time horizon

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£15,513	7.639				96.4%
No treatment	£17,974	7.614	£2,460	-0.025	dominated	2.0%
Metronidazole[(a)]	£18,011	7.615	£2,498	-0.024	dominated	0.9%
Azathioprine	£18,143	7.618	£2,630	-0.021	dominated	0.3%
Mesalazine	£19,007	7.617	£3,493	-0.022	dominated	0.1%
Budesonide	£19,656	7.614	£4,142	-0.025	dominated	0.3%
Mercaptopurine	£21,141	7.636	£5,628	-0.003	dominated	0.0%
INF+MES	£46,247	7.621	£30,733	-0.018	dominated	0.0%
MET+ADA[(a)]	£59,333	7.659	£43,820	0.020	ext. dom.	0.0%
Infliximab	£66,131	7.654	£50,617	0.015	dominated	0.0%
Adalimumab	£69,047	7.685	£53,533	0.046	£1,163,438	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Table 50: Deterministic cost-effectiveness results for scenario 2: lifetime horizon

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£41,281	19.432			
No treatment	£44,442	19.409	£3,160	-0.023	dominated
Metronidazole[(a)]	£44,604	19.410	£3,322	-0.022	dominated
Azathioprine	£45,456	19.413	£4,174	-0.020	dominated
Mesalazine	£45,722	19.412	£4,440	-0.020	dominated
Budesonide	£47,193	19.408	£5,911	-0.024	dominated
Mercaptopurine	£48,552	19.430	£7,270	-0.003	dominated
INF+MES	£75,690	19.417	£34,408	-0.015	dominated
MET+ADA[(a)]	£111,341	19.460	£70,059	0.028	ext. dom.
Infliximab	£112,471	19.449	£71,190	0.017	dominated
Adalimumab	£135,665	19.494	£94,383	0.062	£1,517,426

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab					

(a) Metronidazole administered for 3 months

Table 51: Mean probabilistic cost-effectiveness results for scenario 2: lifetime horizon

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£41,467	19.368				97.2%
No treatment	£44,597	19.343	£3,130	-0.025	dominated	2.2%
Metronidazole[(a)]	£44,787	19.344	£3,320	-0.024	dominated	0.4%
Azathioprine	£45,614	19.347	£4,148	-0.021	dominated	0.0%
Mesalazine	£45,896	19.346	£4,430	-0.022	dominated	0.1%
Budesonide	£47,207	19.344	£5,740	-0.024	dominated	0.1%
Mercaptopurine	£48,714	19.365	£7,247	-0.003	dominated	0.0%
INF+MES	£75,258	19.350	£33,791	-0.017	dominated	0.0%
Infliximab	£111,656	19.383	£70,190	0.015	ext. dom.	0.0%
MET+ADA[(a)]	£112,456	19.398	£70,989	0.031	ext. dom.	0.0%
Adalimumab	£133,663	19.429	£92,196	0.061	£1,499,971	0.0%
MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab						

(a) Metronidazole administered for 3 months

Figure 99: Cost-effectiveness acceptability curve for scenario 2: 10-year time horizon

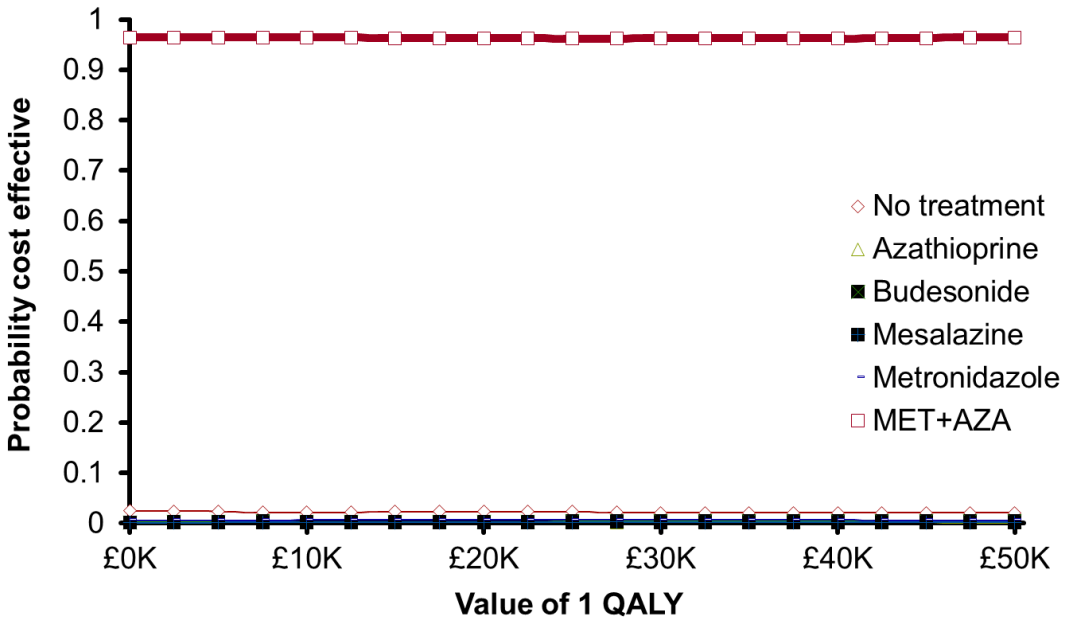
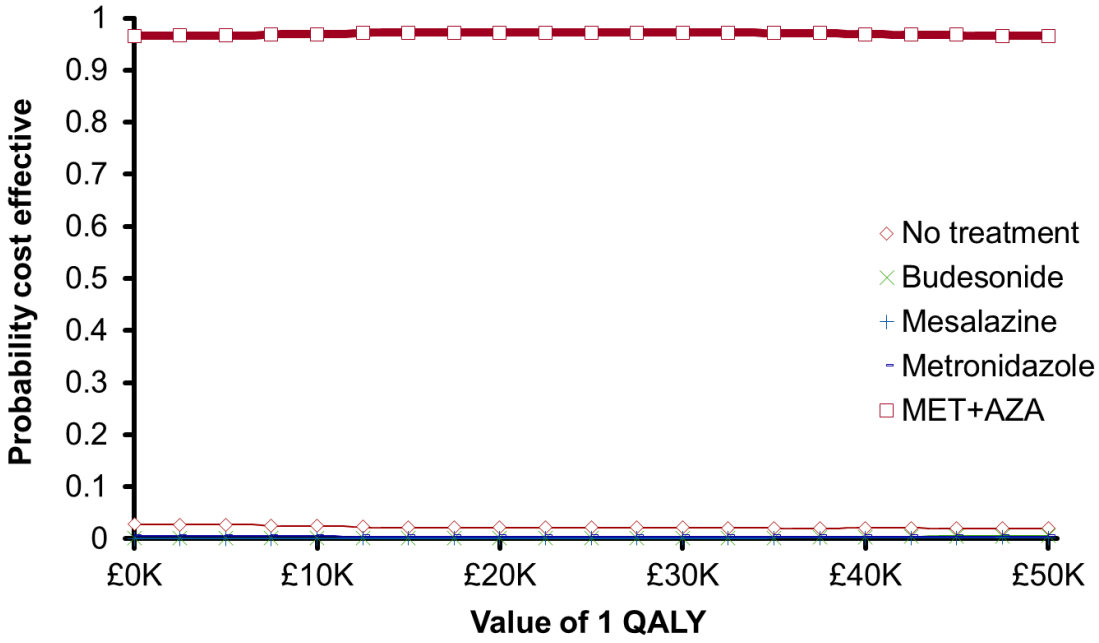


Figure 100: Cost-effectiveness acceptability curve for scenario 2: lifetime time horizon



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 3: Methotrexate as second-line treatment for induction of remission

In this scenario, people whose disease relapses while receiving azathioprine or mercaptopurine for post-surgical maintenance of remission go on to receive methotrexate in combination with a glucocorticosteroid instead of azathioprine if step therapy is required to induce remission. As methotrexate is more expensive than azathioprine, there is a slight increase in the overall cost of the post-surgical maintenance strategies for MET+AZA, azathioprine and mercaptopurine. The deterministic (Table 52) and probabilistic (Table 53) results of the incremental analysis are very similar to the base case. The strategy MET+AZA has the highest probability of being the most cost-effective strategy (92.3%). All other strategies are dominated with the exception of adalimumab, which generates the most QALYs but with an ICER above £850,000/QALY. Figure 101 shows the CEAC for this scenario.

Table 52: Mean deterministic cost-effectiveness results for scenario 3: methotrexate as second-line treatment for induction of remission

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
MET+AZA[(a)]	£5,582	2.673			
Metronidazole[(a)]	£6,726	2.655	£1,145	-0.019	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Azathioprine	£6,799	2.657	£1,217	-0.017	dominated
No treatment	£7,096	2.649	£1,514	-0.025	dominated
Mesalazine	£7,611	2.654	£2,029	-0.020	dominated
Budesonide	£7,984	2.649	£2,402	-0.024	dominated
Mercaptopurine	£8,687	2.668	£3,105	-0.005	dominated
MET+ADA[(a)]	£26,345	2.682	£20,763	0.009	ext. dom.
INF+MES	£27,456	2.670	£21,874	-0.003	dominated
Adalimumab	£28,465	2.699	£22,883	0.025	£904,001
Infliximab	£31,357	2.683	£2,892	-0.016	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

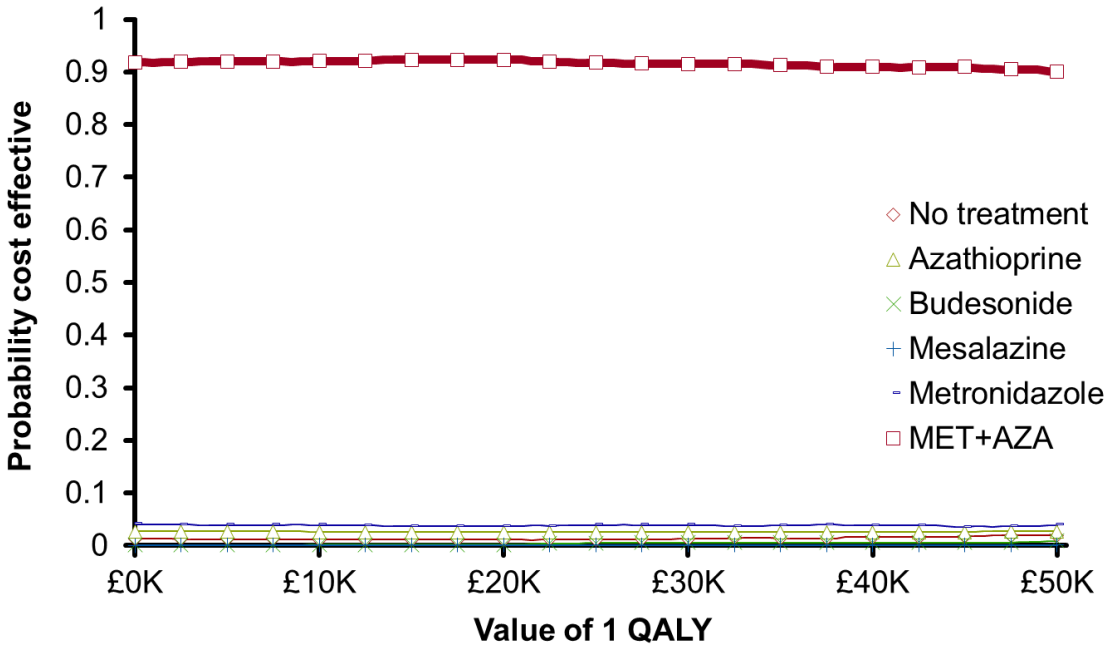
Table 53: Mean probabilistic cost-effectiveness results for scenario 3: methotrexate as second-line treatment for induction of remission

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£5,714	2.677				92.3%
Metronidazole[(a)]	£6,827	2.659	£1,113	-0.018	dominated	3.7%
Azathioprine	£6,914	2.660	£1,200	-0.017	dominated	2.6%
No treatment	£7,206	2.653	£1,492	-0.024	dominated	1.1%
Mesalazine	£7,703	2.658	£1,988	-0.019	dominated	0.1%
Budesonide	£8,088	2.653	£2,373	-0.024	dominated	0.2%
Mercaptopurine	£8,754	2.672	£3,039	-0.005	dominated	0.0%
MET+ADA[(a)]	£25,841	2.683	£20,126	0.007	ext. dom.	0.0%
INF+MES	£27,245	2.673	£21,530	-0.003	dominated	0.0%
Adalimumab	£28,297	2.703	£22,582	0.026	£874,206	0.0%
Infliximab	£31,259	2.687	£2,963	-0.016	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Figure 101: Cost-effectiveness acceptability curve for scenario 3: methotrexate as second-line treatment for induction of remission



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 4: A proportion of patients withdrawing due to adverse events while receiving maintenance treatment transition immediately to active disease

This scenario assumes that 50% of people who withdrew from maintenance treatment due to adverse events will transition directly to an active disease state rather than remain in remission. Deterministic (Table 54) and probabilistic results (Table 55) are similar showing MET+AZA remain the strategy with highest probability of being cost effective (96.1%). Both mercaptopurine and a combination of metronidazole (for 3 months) and adalimumab now form the cost-effectiveness frontier but with ICERs well above £20,000/QALY. The CEAC for this scenario is shown in Figure 102.

Table 54: Deterministic cost-effectiveness results for scenario 4: a proportion of patients withdrawing due to adverse events while receiving maintenance treatment transition immediately to active disease

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£5,531	2.647			
Azathioprine	£6,833	2.641	£1,302	-0.006	dominated
Metronidazole[(a)]	£6,913	2.643	£1,382	-0.005	dominated
No treatment	£7,153	2.648	£1,622	0.001	ext. dom.
Mesalazine	£7,707	2.649	£2,176	0.002	ext. dom.
Budesonide	£8,074	2.648	£2,543	0.001	dominated
Mercaptopurine	£8,637	2.658	£3,106	0.011	£293,498
MET+ADA[(a)]	£26,370	2.680	£17,733	0.022	£800,624

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
INF+MES	£27,661	2.580	£1,291	-0.099	dominated
Adalimumab	£28,441	2.675	£2,071	-0.005	dominated
Infliximab	£31,368	2.657	£4,998	-0.023	dominated

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

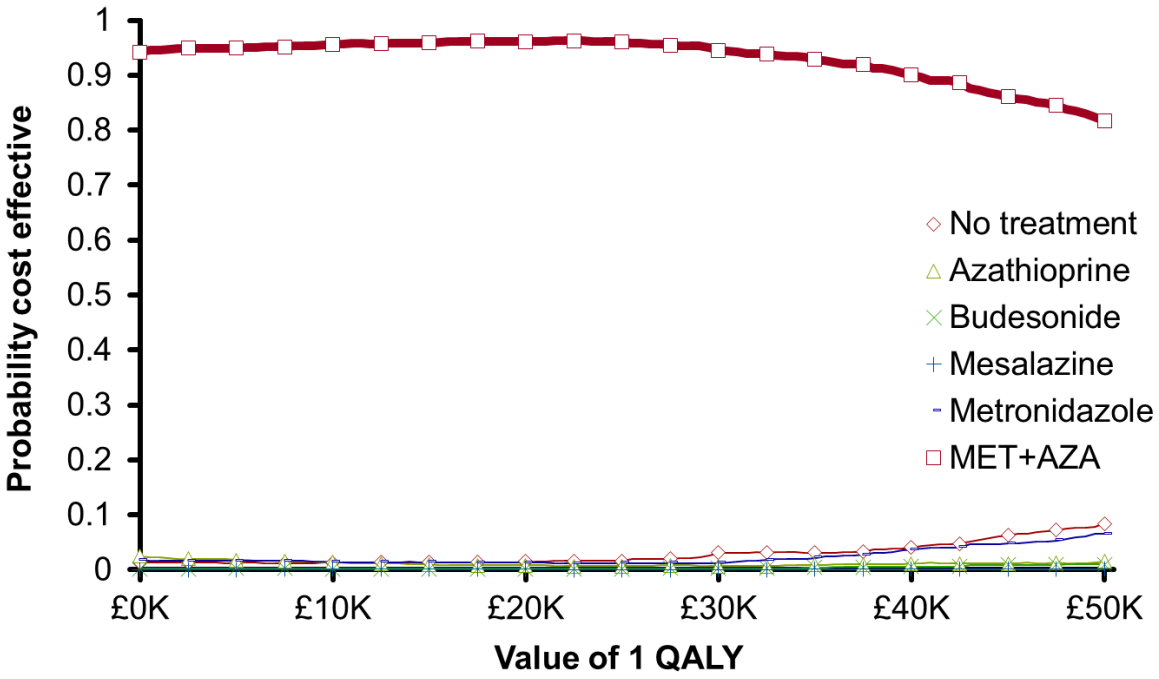
Table 55: Mean probabilistic results for scenario 4: a proportion of patients withdrawing due to adverse events while receiving maintenance treatment transition immediately to active disease

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£5,672	2.651				96.1%
Azathioprine	£6,926	2.644	£1,254	-0.007	dominated	0.8%
Metronidazole[(a)]	£7,014	2.646	£1,342	-0.005	dominated	1.3%
No treatment	£7,250	2.650	£1,578	-0.001	dominated	1.5%
Mesalazine	£7,767	2.652	£2,095	0.001	ext. dom.	0.1%
Budesonide	£8,151	2.650	£2,479	-0.001	dominated	0.2%
Mercaptopurine	£8,690	2.661	£3,018	0.010	£300,689	0.0%
MET+ADA[(a)]	£25,862	2.681	£17,172	0.020	£854,506	0.0%
INF+MES	£27,446	2.588	£1,584	-0.093	dominated	0.0%
Adalimumab	£28,300	2.679	£2,439	-0.002	dominated	0.0%
Infliximab	£31,248	2.660	£5,386	-0.021	dominated	0.0%

MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

Figure 102: Cost-effectiveness acceptability curve for endoscopic relapse with a proportion of patients withdrawing due to adverse events while receiving maintenance treatment transition immediately to active disease



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 5: Apply a disutility for withdrawals due to adverse events

In this scenario, a distulity of -0.05 was applied to all people who withdrew from maintenance treatment due to adverse events. The results are identical to the base-case analysis with MET+AZA having the highest probability of being the best strategy (94.5%). Table 56 and Table 57 show the deterministic and probabilistic results for this scenario. Adalimumab is the most effective strategy as it produces the most total QALYs but has an ICER well in excess of £20,000/QALY. The CEAC is presented in Figure 103.

Table 56: Deterministic results for scenario 5: disutility applied to withdrawals due to adverse events

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
MET+AZA[(a)]	£5,504	2.666			
Azathioprine	£6,684	2.646	£1,180	-0.020	dominated
Metronidazole[(a)]	£6,726	2.642	£1,222	-0.024	dominated
No treatment	£7,096	2.645	£1,591	-0.020	dominated
Mesalazine	£7,611	2.647	£2,107	-0.019	dominated
Budesonide	£7,984	2.644	£2,479	-0.022	dominated
Mercaptopurine	£8,595	2.664	£3,090	-0.002	dominated
MET+ADA[(a)]	£26,345	2.680	£20,840	0.014	ext. dom.
INF+MES	£27,456	2.641	£21,951	-0.025	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Adalimumab	£28,465	2.695	£22,960	0.029	£798,574
Infliximab	£31,357	2.677	£2,892	-0.018	dominated
MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab					

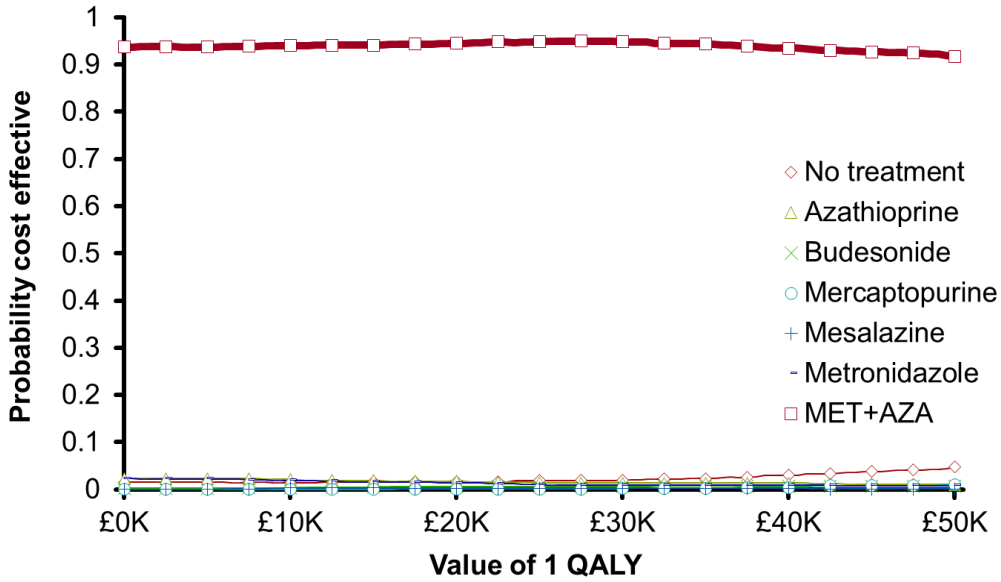
(a) Metronidazole administered for 3 months

Table 57: Mean probabilistic results for scenario 5: disutility applied to withdrawals due to adverse events

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£5,640	2.662				94.5%
Azathioprine	£6,801	2.642	£1,161	-0.020	dominated	1.7%
Metronidazole[(a)]	£6,825	2.639	£1,185	-0.023	dominated	1.3%
No treatment	£7,156	2.643	£1,517	-0.018	dominated	1.6%
Mesalazine	£7,684	2.645	£2,045	-0.017	dominated	0.2%
Budesonide	£8,039	2.643	£2,400	-0.019	dominated	0.6%
Mercaptopurine	£8,651	2.660	£3,012	-0.001	dominated	0.1%
MET+ADA[(a)]	£25,716	2.673	£20,077	0.012	ext. dom.	0.0%
INF+MES	£27,184	2.638	£21,545	-0.024	dominated	0.0%
Adalimumab	£28,271	2.690	£22,632	0.029	£793,728	0.0%
Infliximab	£31,227	2.673	£2,956	-0.017	dominated	0.0%
MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab						

(a) Metronidazole administered for 3 months

Figure 103: Cost-effectiveness acceptability curve for scenario 5: disutility applied to withdrawals due to adverse events



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 6: Continuation of biologic therapy following medically-induced remission beyond 12 months

This scenario assumes that people who respond to infliximab or adalimumab for induction of remission continue to receive these drugs for as long as their disease remains in remission. The results are consistent with the base-case analysis with MET+AZA being the strategy with highest probability of being cost-effective (94.5%). All other strategies are dominated with exception of adalimumab. The ICER associated with adalimumab is well above £20,000/QALY.

Table 58: Deterministic results for scenario 6: continuation of biologic therapy following medically-induced remission beyond 12 months

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
MET+AZA[(a)]	£5,591	2.674			
Azathioprine	£6,817	2.658	£1,226	-0.016	dominated
Metronidazole[(a)]	£6,868	2.655	£1,276	-0.019	dominated
No treatment	£7,273	2.649	£1,681	-0.025	dominated
Mesalazine	£7,766	2.654	£2,174	-0.020	dominated
Budesonide	£8,156	2.650	£2,565	-0.024	dominated
Mercaptopurine	£8,702	2.669	£3,110	-0.005	dominated
MET+ADA[(a)]	£26,417	2.682	£20,825	0.008	ext. dom.
INF+MES	£27,518	2.670	£21,927	-0.004	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Adalimumab	£28,485	2.699	£22,894	0.025	£927,206
Infliximab	£31,418	2.683	£2,933	-0.016	dominated
MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab					

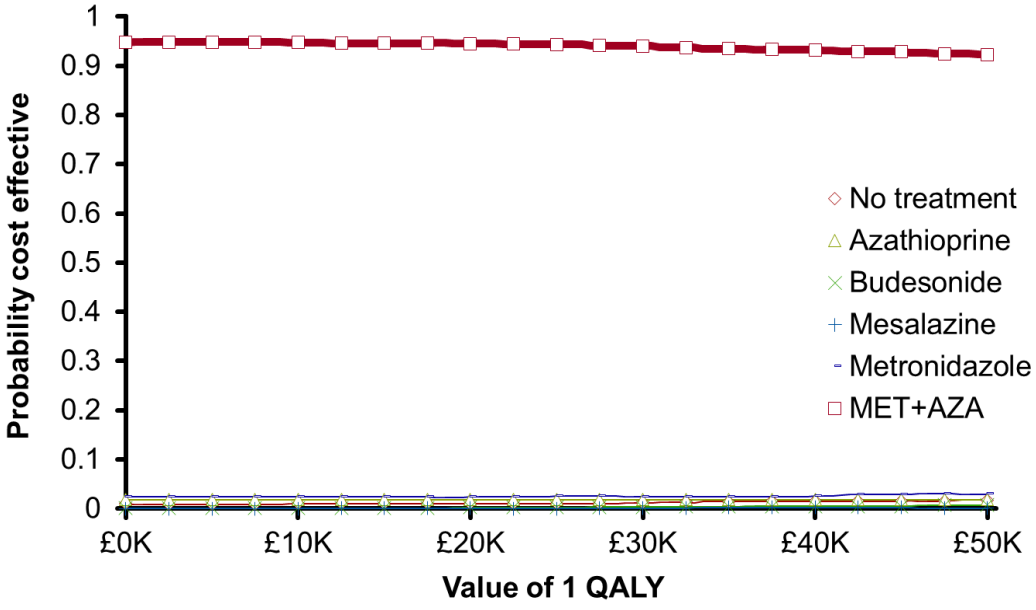
(a) Metronidazole administered for 3 months

Table 59: Mean deterministic results for scenario 6: continuation of biologic therapy medically-induced remission beyond 12 months

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
MET+AZA[(a)]	£5,675	2.651				94.5%
Azathioprine	£6,881	2.635	£1,207	-0.016	dominated	1.8%
Metronidazole[(a)]	£6,946	2.632	£1,271	-0.019	dominated	2.4%
No treatment	£7,323	2.627	£1,648	-0.024	dominated	1.0%
Mesalazine	£7,810	2.631	£2,135	-0.020	dominated	0.1%
Budesonide	£8,181	2.628	£2,506	-0.023	dominated	0.2%
Mercaptopurine	£8,737	2.645	£3,062	-0.005	dominated	0.0%
MET+ADA[(a)]	£25,796	2.657	£20,121	0.007	ext. dom.	0.0%
INF+MES	£27,276	2.646	£21,601	-0.004	dominated	0.0%
Adalimumab	£28,293	2.674	£22,619	0.024	£958,295	0.0%
Infliximab	£31,315	2.660	£3,022	-0.014	dominated	0.0%
MET+AZA = metronidazole in combination with azathioprine; INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab						

(b) Metronidazole administered for 3 months

Figure 104: Cost-effectiveness acceptability curve for scenario 6: continuation of biologic therapy following medically-induced remission beyond 12 months



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 7a: No azathioprine

The committee highlighted that azathioprine intolerance can occur in 10-20% of adults in clinical practice and therefore a scenario analysis was run removing azathioprine from the decision space. This meant not only removing azathioprine as a treatment strategy for post-surgical maintenance of remission, but also removing it as a treatment strategy from downstream parts of the pathway. For second-line induction of remission, the model assumed methotrexate would be given in combination with glucocorticosteroids and for maintenance of medically-induced remission, it was assumed that people would receive mercaptopurine. Deterministic (Table 60) and probabilistic (Table 61) results are consistent with metronidazole alone now having the highest probability of being cost effective (64.9%). Mercaptopurine and adalimumab strategies generate the most QALYs but with ICERs above £20,000/QALY. All other strategies are dominated. Figure 105 presents the CEAC for this scenario.

Table 60: Deterministic results for scenario 7a: no azathioprine

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Metronidazole[(a)]	£7,975	2.654			
No treatment	£8,584	2.648	£609	-0.006	dominated
Mesalazine	£8,939	2.653	£964	-0.001	dominated
Budesonide	£9,340	2.648	£1,365	-0.006	dominated
Mercaptopurine	£9,531	2.668	£1,556	0.014	£108,282
MET+ADA[(a)]	£26,985	2.682	£17,455	0.013	ext. dom.
INF+MES	£28,167	2.670	£18,636	0.001	dominated
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394
Infliximab	£31,935	2.683	£3,265	-0.016	dominated

INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab

(a) Metronidazole administered for 3 months

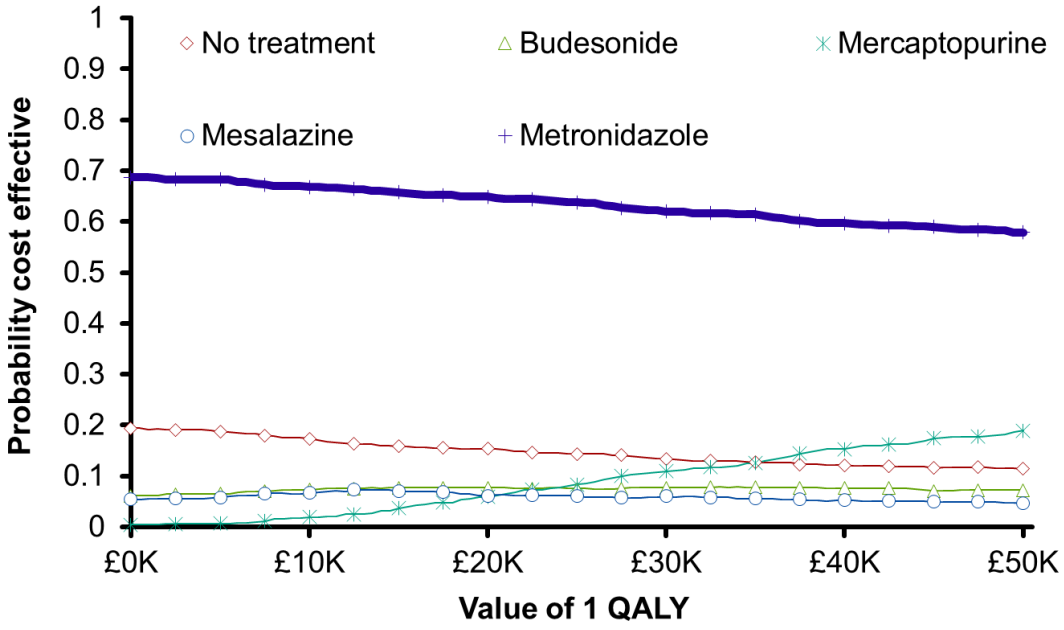
Table 61: Mean probabilistic results for scenario 7a: no azathioprine

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	
Metronidazole[(a)]	£8,104	2.662				64.9%
No treatment	£8,668	2.657	£564	-0.006	dominated	15.4%
Mesalazine	£9,024	2.662	£920	-0.001	dominated	6.1%
Budesonide	£9,434	2.657	£1,330	-0.006	dominated	7.7%
Mercaptopurine	£9,610	2.677	£1,506	0.015	£100,624	5.9%
MET+ADA[(a)]	£26,490	2.688	£16,881	0.011	ext. dom.	0.0%
INF+MES	£27,957	2.678	£18,347	0.001	dominated	0.0%
Adalimumab	£28,549	2.709	£18,939	0.032	£598,894	0.0%
Infliximab	£31,814	2.693	£3,266	-0.016	dominated	0.0%

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
INF+MES = infliximab in combination with mesalazine; MET+ADA = metronidazole in combination with adalimumab						

(a) Metronidazole administered for 3 months

Figure 105: Cost-effectiveness acceptability curve for scenario 7a: no azathioprine



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 7b: No azathioprine and no metronidazole

Similar to azathioprine, metronidazole may be poorly tolerated by some people. If strategies containing either of these drugs are removed from the decision space, no treatment becomes the strategy with the highest probability of being cost effective (50.5%). No treatment dominates all comparators except mercaptopurine and adalimumab but both of these options generate ICERs above £20,000/QALY. Figure 106 presents the CEAC for this scenario.

Table 62: Deterministic results for scenario 7b: no azathioprine and no metronidazole

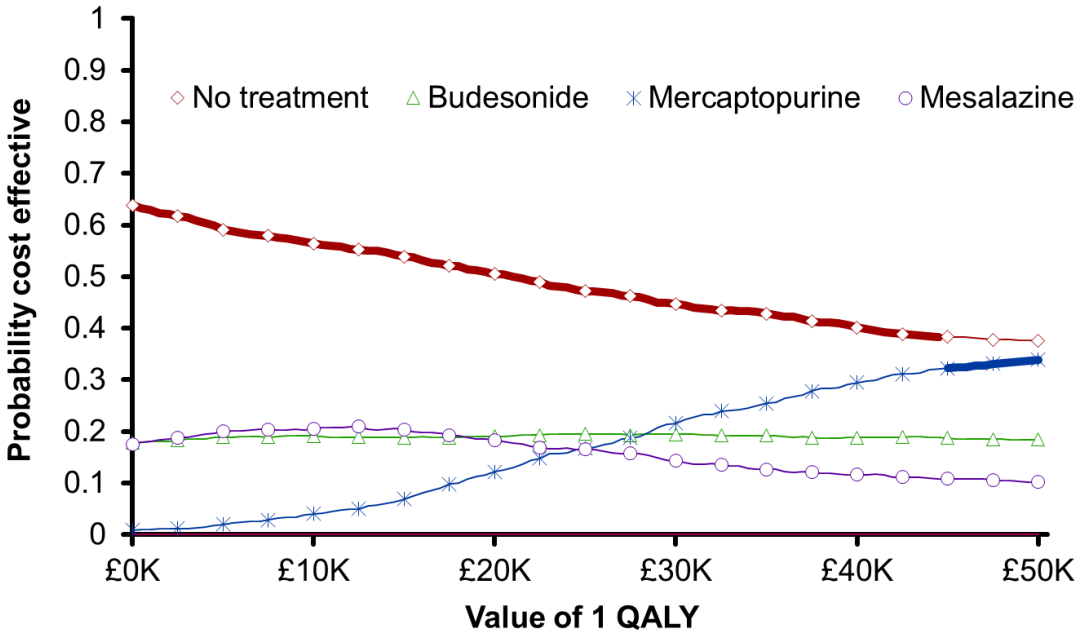
Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
No treatment	£8,584	2.648			
Mesalazine	£8,939	2.653	£355	0.005	ext. dom.
Budesonide	£9,340	2.648	£757	0.000	dominated
Mercaptopurine	£9,531	2.668	£947	0.020	£46,637
INF+MES	£28,167	2.670	£18,636	0.001	ext. dom.
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Infliximab	£31,935	2.683	£3,265	-0.016	dominated
IINF+MES = infliximab in combination with mesalazine					

Table 63: Mean probabilistic results for scenario 7b: no azathioprine and no metronidazole

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
No treatment	£8,704	2.639				50.5%
Mesalazine	£9,075	2.644	£371	0.005	ext. dom.	18.3%
Budesonide	£9,444	2.639	£741	0.000	dominated	19.0%
Mercaptopurine	£9,638	2.660	£935	0.021	£44,600	12.2%
INF+MES	£27,988	2.661	£18,350	0.001	ext. dom.	0.0%
Adalimumab	£28,526	2.691	£18,887	0.031	£600,073	0.0%
Infliximab	£31,853	2.675	£3,327	-0.016	dominated	0.0%
INF+MES = infliximab in combination with mesalazine						

Figure 106: Cost-effectivenessa acceptability curve for scenario 7b: no azathioprine and no metronidazole



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 7c: No metronidazole

The deterministic results for the scenario with no metronidazole are shown in Table 64. These are consistent with the probabilistic results (Table 65) with azathioprine having the highest probability of being cost effective (72.0%) and dominating all other strategies except mercaptopurine and adalimumab. These strategies generated more total QALYs than azathioprine alone but had ICERs above £20,000/QALY. The CEAC for this scenario is shown in Figure 107.

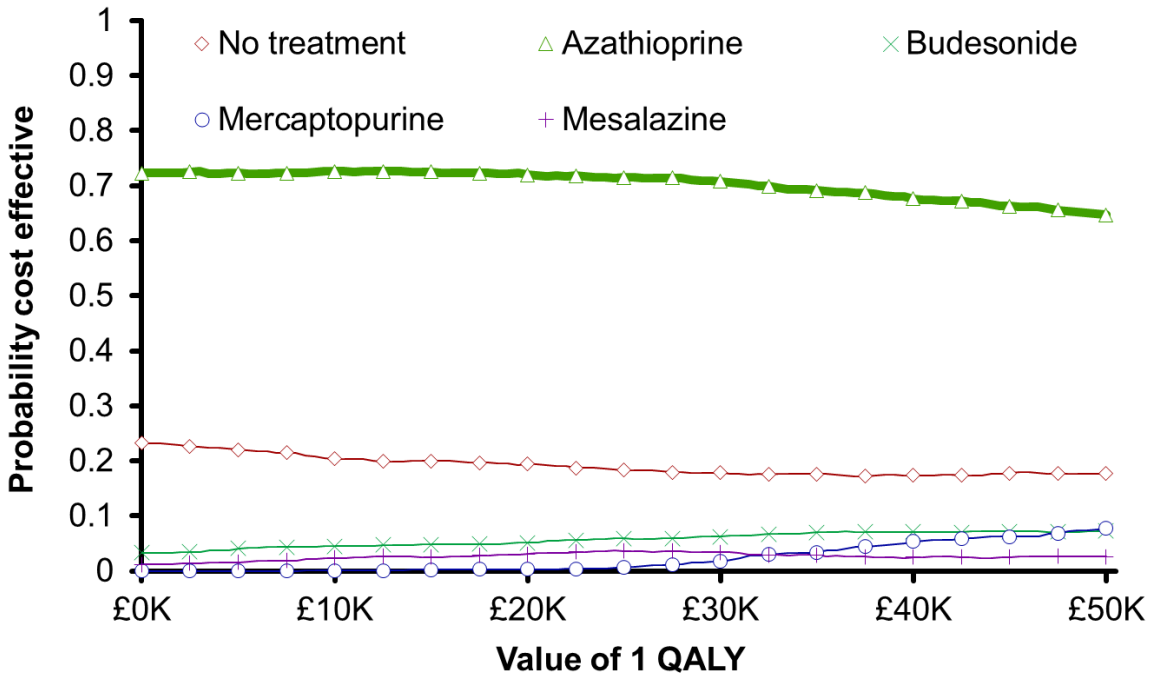
Table 64: Deterministic results scenario 7c: no metronidazole

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
Azathioprine	£6,684	2.658			
No treatment	£7,096	2.649	£412	-0.009	dominated
Mesalazine	£7,611	2.654	£927	-0.004	dominated
Budesonide	£7,984	2.649	£1,300	-0.008	dominated
Mercaptopurine	£8,595	2.669	£1,910	0.011	£167,707
INF+MES	£27,456	2.670	£18,861	0.001	ext. dom.
Adalimumab	£28,465	2.699	£19,870	0.030	£665,175
Infliximab	£31,357	2.683	£2,892	-0.016	dominated
INF+MES = infliximab in combination with mesalazine					

Table 65: Mean probabilistic results for scenario 7c: no metronidazole

	Absolute		Incremental			Prob CE at £20k/QALY
Strategy	Costs	QALYs	Costs	QALYs	ICER	
Azathioprine	£6,779	2.643				72.0%
No treatment	£7,155	2.635	£376	-0.008	dominated	19.5%
Mesalazine	£7,674	2.640	£895	-0.003	dominated	3.1%
Budesonide	£7,992	2.636	£1,213	-0.007	dominated	5.1%
Mercaptopurine	£8,644	2.654	£1,865	0.011	£167,993	0.3%
INF+MES	£27,171	2.655	£18,527	0.001	ext. dom.	0.0%
Adalimumab	£28,288	2.684	£19,643	0.029	£673,636	0.0%
Infliximab	£31,242	2.669	£2,955	-0.014	dominated	0.0%
INF+MES = infliximab in combination with mesalazine;						

Figure 107: Cost-effectiveness acceptability curve for scenario 7c: no metronidazole



The bold line indicates the cost-effectivess acceptability frontier.

Scenario 7d: No azathioprine, no metronidazole and no mesalazine

There was some uncertainty about the clinical benefit of mesalazine for maintaining endoscopic remission in the NMA. In this scenario, ICERs were recalculated after removing azathioprine, metronidazole and mesalazine from the decision space. The deterministic and probabilistic results are shown in Table 66 and Table 67. No treatment now has the highest probability of being cost effective (59.4%) and dominates all strategies except mercaptopurine and adalimumab. However, the ICERs for both of these strategies are above £20,000/QALY. The CEAC for this scenario is shown in Figure 7.

It was noted that the cost per pack of mercaptopurine had more than doubled since the 2012 guideline. Therefore, an exploratory analysis was run to estimate the cost at which mercaptopurine would become cost effective assuming a threshold of £20,000/QALY. This analysis found that the ICER for mercaptopurine compared to no treatment would fall to £20,000/QALY at a cost of £36.67 per pack (£3.93 per day), which represents a 25% discount to the current list price of £49.15 (£2.93 per day).

Table 66: Deterministic results for scenario 7d: no azathioprine, no metronidazole and no mesalazine

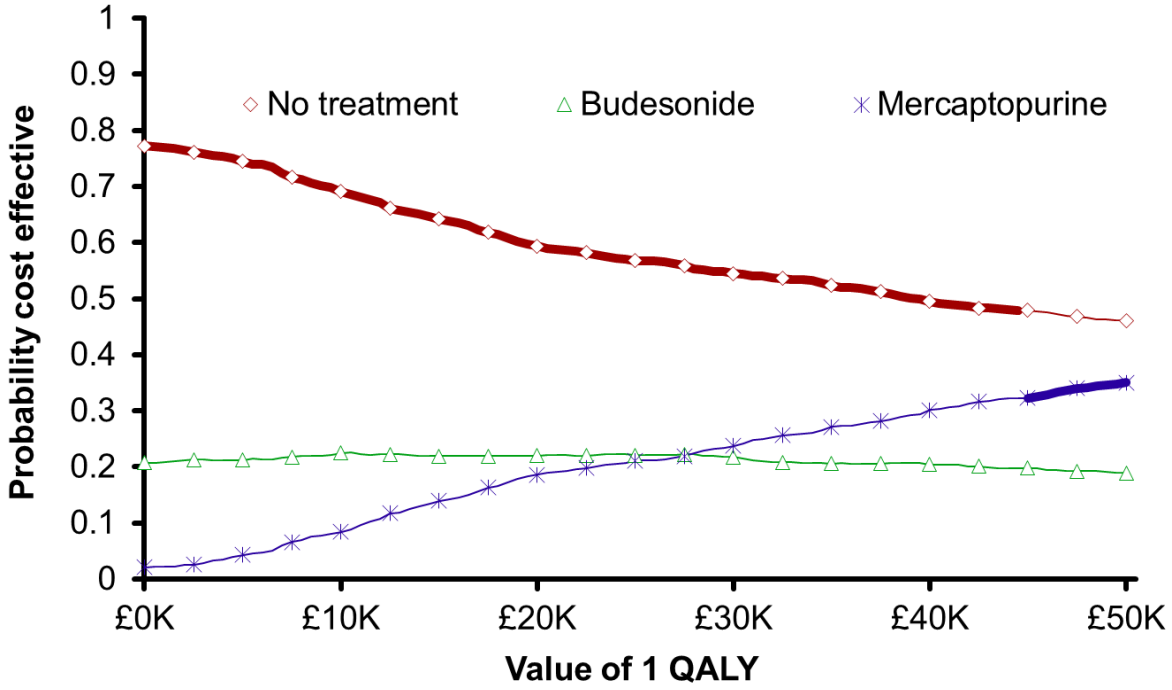
	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER
No treatment	£8,584	2.648			
Budesonide	£9,340	2.648	£757	0.000	ext. dom.
Mercaptopurine	£9,531	2.668	£947	0.020	£46,637

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
INF+MES	£28,167	2.670	£18,636	0.001	ext. dom.
Adalimumab	£28,671	2.699	£19,140	0.030	£632,394
Infliximab	£31,935	2.683	£3,265	-0.016	dominated
INF+MES = infliximab in combination with mesalazine					

Table 67: Mean probabilistic results for scenario 7d: no azathioprine, no metronidazole and no mesalazine

Strategy	Absolute		Incremental			Prob CE at £20k/QALY
	Costs	QALYs	Costs	QALYs	ICER	
No treatment	£8,655	2.651				59.4%
Budesonide	£9,371	2.653	£717	0.002	ext. dom.	22.0%
Mercaptopurine	£9,583	2.672	£928	0.021	£44,830	18.6%
INF+MES	£27,938	2.672	£18,356	0.000	ext. dom.	0.0%
Adalimumab	£28,507	2.701	£18,924	0.030	£639,540	0.0%
Infliximab	£31,851	2.686	£3,344	-0.015	dominated	0.0%
INF+MES = infliximab in combination with mesalazine;						

Figure 108: Cost-effectiveness acceptability curve for scenario 7d: no azathioprine, no metronidazole and no mesalazine



The bold line indicates the cost-effectivess acceptability frontier.

Discussion

Main findings

The results of the original economic model showed that in the base case endoscopic relapse analysis, the combination of metronidazole given for 3 months and azathioprine was the most cost-effective strategy. The committee noted that the differences in QALYs between treatment strategies were generally small while the differences in costs between treatment strategies ranged from £1,000 to more than £22,000 in the base case. The results reflect the nature of maintenance treatment in which the entire cohort starts off in a state of remission receiving continuous treatment until withdrawal or relapse; maintenance treatment has not been shown to have a direct impact on Crohn's disease-related mortality and therefore in the model, the QALY differences between treatments are mainly driven by the difference in health status for people whose disease is active or in remission and by the relative proportions of people in these states over the time frame of the analysis.

In most people, endoscopic relapse precedes clinical relapse, which means there can be evidence of recurrence of lesions even in the absence of symptoms. The committee discussed that over time, the objectives of treatment in Crohn's disease has shifted away from symptom relief alone towards mucosal healing as a better indicator of long-term

outcomes and the need for further surgery. For this reason, the committee prioritised endoscopic relapse as the most important outcome for this review question but also considered clinical or symptomatic relapse to be a relevant outcome of interest. A scenario analysis was run in the cost-effectiveness model using data on clinical relapse (both baseline and relative treatment effects) instead of endoscopic relapse. This resulted in greater uncertainty about the optimal strategy but overall, the combination of metronidazole given for 3 months plus azathioprine remained the most cost-effective strategy.

The committee felt that 3 years was the most appropriate time frame for the base case analysis because this reflected the longest duration of follow-up that was available across several RCTs. They were uncertain if adherence to treatment and the relative effectiveness of treatments could be assumed to remain constant beyond this period. However, there was also recognition that the downstream costs and benefits of maintenance treatment could extend beyond 3 years if more effective treatments continue to delay disease relapse and the need for further treatment and reoperation. Scenario analyses were conducted to explore a 10-year and a lifetime time horizon but did not result in any changes to the overall conclusions.

In the base-case analysis, it was assumed people who withdrew from maintenance treatment due to adverse events would initially remain in remission but would face a higher risk of relapse associated with no treatment. In practice, there is considerable heterogeneity in the reporting of withdrawals due to adverse events across RCTs and it is plausible that some reporting of withdrawals may overlap with symptoms of disease recurrence. Therefore, a scenario analysis was run assuming that 50% of patients who withdrew from maintenance treatment experienced immediate relapse (active disease) while the other 50% initially remained in remission. This resulted in a small reduction in QALYs for most strategies but overall, the combination of metronidazole given for 3 months and azathioprine remained the most cost-effective strategy.

In the model, people whose disease relapsed following surgery were assumed to require further treatment to induce remission. In the first instance, people would receive a conventional glucocorticosteroid. If remission is not achieved with a glucocorticosteroid, the model assumed azathioprine or mercaptopurine would be added to the glucocorticosteroid to induce remission. However, for people whose disease relapsed while receiving azathioprine or mercaptopurine as treatment for post-surgical maintenance of remission, it is unlikely that the same drug would be used again to induce remission. A scenario analysis was conducted assuming these people would receive methotrexate to induce remission instead. Although the cost of methotrexate per 2-monthly cycle is more than 10-fold the cost of azathioprine, this did not lead to an overall change in the conclusions of the analysis. In people who received infliximab or adalimumab to induce remission, the base-case model assumed those who responded to initial treatment would continue to receive a 12-month planned course and then stop. A scenario analysis was run in which people were assumed to continue receiving biologic therapy beyond 12 months. Again, this did not lead to an overall change in the conclusions of the analysis.

The cost effectiveness of treatments for post-operative maintenance of remission in people intolerant to azathioprine and metronidazole was explored by removing these agents from the model, in turn and simultaneously. When azathioprine was removed, metronidazole alone became the most cost-effective strategy. When metronidazole was removed from the decision space, azathioprine alone became the most cost-effective strategy. When both azathioprine and metronidazole were removed, no treatment became the most cost-effective strategy. All of these scenarios were associated with a higher degree of uncertainty than the

base case. The committee was concerned that in clinical practice, uptake of metronidazole on its own would be low due to side effects. As a result, the committee did not feel there was a strong case for metronidazole to be recommended. An additional scenario with no azathioprine, no metronidazole and no mesalazine was explored. In this scenario, no treatment became the most cost-effective strategy. Despite generating more total QALYs than the no treatment strategy, mercaptopurine and adalimumab both had ICERs above £20,000/QALY. An exploratory analysis found that the ICER for mercaptopurine compared to no treatment would fall to £20,000/QALY at a 25% discount to the current list price.

Strengths

The main strength of this analysis is that it made use of all available data to compare as many treatments as possible using the outputs of the network meta-analyses. This enabled an assessment of the cost effectiveness of a number of drugs that had not previously been compared in the same decision space.

While other cost-effectiveness analyses of treatments for post-surgical maintenance of remission have focussed on clinical relapse as the main outcome, this analysis used data on endoscopic relapse in the base case. The committee felt this reflected an important shift in clinical practice towards more emphasis on earlier intervention to promote mucosal healing rather than symptom relief alone.

Previous cost-effective models have adopted short time horizons of 1 year in the base case and may not have captured longer-term costs and benefits associated with different post-surgical treatments for maintenance of remission. In our analysis, we were able to include a number of trials with longer-term follow-up and adopted a 3-year time horizon for the base case analysis. The committee felt there was increasing uncertainty about adherence to treatment and whether the relative effectiveness of treatments would be maintained beyond this period. We were able to demonstrate that if treatment effects remained constant, extending the time horizon beyond 3 years did not change the overall conclusions of the analysis.

Limitations

There are a number of important assumptions and limitations to note with respect to this analysis. Firstly, to estimate relative treatment effects in the NMAs that informed the cost-effectiveness model, it was necessary to assume that hazard ratios were constant for all outcomes. Insufficient data were available to test alternative assumptions. In addition, some of the estimates of relative effects from the NMA were subject to considerable uncertainty due to sparseness of the network and small sample sizes of a number of trials. This was especially true for the outcome withdrawal due to adverse events.

Secondly, we were unable to explicitly model the impact of treatment-specific adverse events in the cost-effectiveness model. This would require consistent reporting of data for specific adverse events across trials as well as estimates of the impact of adverse events on health-state utilities. In the absence of this information, withdrawal due to adverse events was used as a proxy. In addition, a scenario analysis was run in which a disutility of -0.05 was applied to all people who withdrew from post-surgical maintenance treatment due to adverse events.

Thirdly, for people whose disease relapsed while on maintenance treatment, the structure of the economic model assumed they will receive further treatment to induce remission in accordance with recommendations made elsewhere in this guideline. This includes step-up

treatment with conventional glucocorticosteroids in the first instance followed by the addition of azathioprine or mercaptopurine if remission is not achieved and then a TNF inhibitor (infliximab or adalimumab) and finally reoperation. The committee noted that in clinical practice, a number of other treatment options would be considered before reoperation, including dose escalation or switching between TNF inhibitors and other biologic therapies (vedolizumab and ustekinumab). However, there was uncertainty about the optimal strategy and consistency in clinical practice with respect to these options so they were not explicitly modelled as part of the downstream pathway. It was acknowledged that these additional options could further delay the need for reoperation and incur high costs but that the proportion of people affected in the model would be small and unlikely to change the conclusions of the analysis.

Finally, the committee noted the high drug costs for infliximab and adalimumab in the base case model and felt that these do not necessarily reflect locally negotiated prices. We explored the impact of reducing the cost per dose for both drugs by 25%, 50% and 75% and found that this did not change the overall conclusions.

Comparison with other cost-effectiveness analyses

A search of the published literature identified 2 cost-utility analyses that each compared a subset of the drugs of relevance to the review question. Ananthakrishnan 2011 compared no treatment, azathioprine, mercaptopurine and 2 infliximab strategies (upfront and tailored) for post-surgical maintenance of clinical remission of Crohn's disease. Metronidazole was found to be the dominant treatment strategy. Doherty 2012 compared 4 treatment strategies for post-surgical maintenance of clinical remission of Crohn's disease: no treatment, mesalazine, azathioprine/mercaptopurine and infliximab. The no treatment strategy was associated with the highest net health benefit up to a threshold of $245,000 (£186,000)/QALY.

Both of these published studies were conducted in the context of the US healthcare system, focussed on clinical relapse data and adopted a 1-year time horizon. Despite differences in data inputs and model assumptions in comparison to our analysis, some similarities in results were noted, namely that the QALY differences between treatment strategies were very small and that, although biologic therapies (infliximab and adalimumab) generated the most QALYs, the large incremental cost differences resulted in ICERs that were well in excess of conventional threshold values.

Conclusions

A cost-effectiveness analysis was conducted to compare different treatment strategies for post-surgical maintenance of remission of Crohn's disease. The combination of metronidazole plus azathioprine had the highest probability of being the most cost-effective strategy, a finding that was consistent across a range of scenario analyses.

Appendix M: Excluded studies

Clinical studies

Short Title	Reason for exclusion
Allocca (2017)	Not a randomised controlled trial. Surgery occurred more than 3 months prior to commencing treatment.
Angelberger (2013)	Post-hoc analysis of a previously excluded study.
Bakouny (2018)	Systematic review/meta-analysis used to check references.
Beaupel (2017)	Not a randomised controlled trial. Intervention not included (oral nutrition)
Behm (2008)	Systematic review/meta-analysis used to check references.
Carla-Moreau (2015)	Systematic review/meta-analysis used to check references.
Carla-Moreau (2015)	Systematic review/meta-analysis used to check references.
Cruz (2015)	Study design does not address review question. Randomisation to different post-operative procedures (colonoscopy or standard care).
de Souza (2013)	Population is not confined to post-surgery Crohn's disease.
Doherty (2009)	Systematic review/meta-analysis used to check references.
Doherty (2010)	Systematic review/meta-analysis used to check references.
El-Hussuna (2014)	Systematic review/meta-analysis used to check references.
Feagan (2015)	Abstract, not post-surgery specific.
Feng (2017)	Systematic review/meta-analysis used to check references.
Ferrante (2014)	Abstract.
Ferrante (2015)	Comparison not included
Gordon (2014)	Systematic review/meta-analysis used to check references.
Hadigan (1999)	Abstract.
Hanai (2012)	Population is not confined to post-surgery Crohn's disease.
Kawalec (2013)	Systematic review/meta-analysis used to check references.
Kopylov (2012)	Systematic review/meta-analysis used to check references.
Kuenzig (2014)	Systematic review/meta-analysis used to check references.
Loo (2012)	Abstract.
Matsumoto (2016)	Outcomes are not reported in a useable format.
Nguyen (2014)	Systematic review/meta-analysis used to check references.
Papamichael (2012)	Study design does not address review question.
Papi (2012)	Systematic review/meta-analysis used to check references.
Patel (2014)	Systematic review/meta-analysis used to check references.

Qiu (2015)	Systematic review/meta-analysis used to check references.
Regueiro (2011)	Secondary publication of included study with no additional evidence provided.
Regueiro (2014)	Open-label follow-up of included RCT.
Regueiro (2015)	Abstract.
Rutgeerts (2006)	Study design does not address review question.
Singh (2015)	Systematic review/meta-analysis used to check references.
Sutherland (1997)	Randomised treatment duration is less than 12 months.
Van Assche (2012)	Population is not confined to post-surgery Crohn's disease.
van Loo (2012)	Systematic review/meta-analysis used to check references.
Waterland (2016)	Systematic review/meta-analysis used to check references.
Yamamoto (2007)	Not a randomised controlled trial.
Yamamoto (2013)	Not a randomised controlled trial.
Yang (2014)	Systematic review/meta-analysis used to check references.
Yassin (2014)	Systematic review/meta-analysis used to check references.
Zhao (2015)	Systematic review/meta-analysis used to check references.

Excluded studies from top-up search

Short Title	Reasons for exclusion
Allez (2018)	Abstract
Bakouny (2018)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Berends (2018)	Abstract
Chalhoub (2017)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Colman (2018)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Dziechciarz (2016)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
El-Matary (2017)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.Intervention not included in evidence review.
Engel (2018)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Estevinho (2017)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Feagan (2018)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Fukushima (2018)	Outcome data could not be ascertained.
Ganji-Arjenaki (2018)	Systematic review/meta-analysis which does not meet criteria of protocol.
Ghosh (2018)	Abstract

Short Title	Reasons for exclusion
Ghosh (2018)	Abstract
Gordon (2014)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Hardi (2018)	Abstract
Kuenzig (2014)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Lev-Tzion (2014)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.Intervention not included in evidence review.
Lopez-Sanroman (2017)	Included in evidence review.
Ma (2018)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Mowat (2016)	Included in evidence review.
Panaccione (2018)	Abstract
Patel (2014)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Roblin (2017)	Comparison not included in evidence review.
Sandborn (2018)	Indirect population - not post-surgery.
Satsangi (2017)	Secondary publication of included study.
Schlussel (2017)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Shen (2012)	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Vermeire (2018)	Abstract
Walters (2017)	Indirect population - not post-surgery.
Zarubova (2017)	Not a randomised controlled trial.

Economic studies

Author	Title	Reason for exclusion
Bodger 2009	Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data.	Not in the postoperative setting (patients had active disease).
Candia 2017	Cost-utility analysis: thiopurines plus endoscopy-guided biological step-up therapy is the optimal management of postoperative Crohn's disease.	Comparator outside scope of interventions for the review question (endoscopy-guided biological step-up therapy); societal perspective, 5% discount rate
Wright 2015	Effect of intestinal resection on quality of life in Crohn's disease.	Not a full economic evaluation. Assesses quality of life before and after surgery for Crohn’s disease.

Appendix N: Research recommendations

Question	What are the benefits, risk and cost effectiveness of enteral nutrition in maintaining remission in the post-surgical period of Crohn's disease?
Population	People who have had surgery for their Crohn's disease in the past 12 weeks
Intervention	Enteral nutrition, either alone or in combination.
Comparator	Placebo or intervention alone (if compared to enteral nutrition plus intervention).
Outcomes	• Maintenance of endoscopic remission • Maintenance of clinical remission • Adverse events • Withdrawal due to adverse events • Quality of life
Study design	Randomised Controlled Trial
Potential criterion	**Explanation**
Importance to patients, service users or the population	Enteral nutrition may have an impact on the maintenance of remission after surgery. It may also improve patient's quality of life if it has an effect on symptoms.
Relevance to NICE guidance	The committee noted that this was an important area of research, as it is considered in maintenance of remission after surgery, particularly in children. The committee was unable to make recommendations due to the lack of evidence. Further research would enable future updates to make recommendations in this area.
Current evidence base	There was no evidence on enteral nutrition found from randomised controlled trials.
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people who have surgery for their Crohn's disease and who may receive enteral nutrition as part of their care pathway that a study of this type is feasible.