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Interventions for maintenance of surgically induced remission in Crohn's disease: a network meta-analysis (Review)

Iheozor-Ejiofor Z, Gordon M, Clegg A, Freeman SC, Gjuladin-Hellon T, MacDonald JK, Akobeng AK

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[Intervention Review]

Interventions for maintenance of surgically induced remission in Crohn's disease: a network meta-analysis

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ABSTRACT

Background

Crohn's disease (CD) is a chronic disease of the gut. About 75% of people with CD undergo surgery at least once in their lifetime to induce remission. However, as there is no known cure for the disease, patients usually experience a recurrence even after surgery. Different interventions are routinely used in maintaining postsurgical remission. There is currently no consensus on which treatment is the most effective.

Objectives

To assess the effects and harms of interventions for the maintenance of surgically induced remission in Crohn's disease and rank the treatments in order of effectiveness.

Search methods

We searched the Cochrane IBD Group Specialized Register, CENTRAL, MEDLINE, and Embase from inception to 15 January 2019. We also searched reference lists of relevant articles, abstracts from major gastroenterology meetings, ClinicalTrials.gov, and the WHO ICTRP. There was no restriction on language, date, or publication status.

Selection criteria

We considered for inclusion randomised controlled trials (RCTs) that compared different interventions used for maintaining surgically induced remission in people with CD who were in postsurgical remission. Participants had to have received maintenance treatment for at least three months. We excluded studies assessing enteral diet, diet manipulation, herbal medicine, and nutritional supplementation.

Data collection and analysis

Two review authors independently selected relevant studies, extracted data, and assessed the risk of bias. Any disagreements were resolved by discussion or by arbitration of a third review author when necessary. We conducted a network meta-analysis (NMA) using a Bayesian approach through Markov Chain Monte Carlo (MCMC) simulation. For the pairwise comparisons carried out in Review Manager 5, we calculated risk ratios (RR) with their corresponding 95% confidence intervals (95% CI). For the NMA, we presented hazard ratios (HR) with corresponding 95% credible intervals (95% CrI) and reported ranking probabilities for each intervention. For the NMA,

we focused on three main outcomes: clinical relapse, endoscopic relapse, and withdrawals due to adverse events. Data were insufficient to assess time to relapse and histologic relapse. Adverse events and serious adverse events were not sufficiently or objectively reported to permit an NMA. We used CINeMA (Confidence in Network Meta-Analysis) methods to evaluate our confidence in the findings within networks, and GRADE for entire networks.

Main results

We included 35 RCTs (3249 participants) in the review. The average age of study participants ranged between 33.6 and 38.8 years. Risk of bias was high in 18 studies, low in four studies, and unclear in 13 studies. Of the 35 included RCTs, 26 studies (2581 participants; 9 interventions) were considered eligible for inclusion in the NMA. The interventions studied included 5-aminosalicylic acid (5-ASA), adalimumab, antibiotics, budesonide, infliximab, probiotics, purine analogues, sulfasalazine, and a combination of sulfasalazine and prednisolone. This resulted in 30 direct contrasts, which informed 102 mixed-treatment contrasts.

The evidence for the clinical relapse network (21 studies; 2245 participants) and endoscopic relapse (12 studies; 1128 participants) were of low certainty while the evidence for withdrawal due to adverse events (15 studies; 1498 participants) was of very low certainty. This assessment was due to high risk of bias in most of the studies, inconsistency, and imprecision across networks. We mainly judged individual contrasts as of low or very low certainty, except 5-ASA versus placebo, the evidence for which was judged as of moderate certainty.

We ranked the treatments based on effectiveness and the certainty of the evidence. For clinical relapse, the five most highly ranked treatments were adalimumab, infliximab, budesonide, 5-ASA, and purine analogues. We found some evidence that adalimumab (HR 0.11, 95% Crl 0.02 to 0.33; low-certainty evidence) and 5-ASA may reduce the probability of clinical relapse compared to placebo (HR 0.69, 95% Crl 0.53 to 0.87; moderate-certainty evidence). However, budesonide may not be effective in preventing clinical relapse (HR 0.66, 95% CrI 0.27 to 1.34; low-certainty evidence). We are less confident about the effectiveness of infliximab (HR 0.36, 95% CrI 0.02 to 1.74; very low-certainty evidence) and purine analogues (HR 0.75, 95% CrI 0.55 to 1.00; low-certainty evidence). It was unclear whether the other interventions reduced the probability of a clinical relapse, as the certainty of the evidence was very low.

Due to high risk of bias and limited data across the network, we are uncertain about the effectiveness of interventions for preventing endoscopic relapse. Whilst there might be some evidence of prevention of endoscopic relapse with adalimumab (HR 0.10, 95% CrI 0.01 to 0.32; low-certainty evidence), no other intervention studied appeared to be effective.

Due to high risk of bias and limited data across the network, we are uncertain about the effectiveness of interventions for preventing withdrawal due to adverse events. Withdrawal due to adverse events appeared to be least likely with sulfasalazine (HR 1.96, 95% Crl 0.00 to 8.90; very low-certainty evidence) and most likely with antibiotics (HR 53.92, 95% Crl 0.43 to 259.80; very low-certainty evidence). When considering the network as a whole, two adverse events leading to study withdrawal (i.e. pancreatitis and leukopenia) occurred in more than 1% of participants treated with an intervention. Pancreatitis occurred in 2.8% (11/399) of purine analogue participants compared to 0.17% (2/1210) of all other groups studied. Leukopenia occurred in 2.5% (10/399) of purine analogue participants compared to 0.08% (1/1210) of all other groups studied.

Authors' conclusions

Due to low-certainty evidence in the networks, we are unable to draw conclusions on which treatment is most effective for preventing clinical relapse and endoscopic relapse. Evidence on the safety of the interventions was inconclusive, however cases of pancreatitis and leukopenia from purine analogues were evident in the studies. Larger trials are needed to further understand the effect of the interventions on endoscopic relapse.

PLAIN LANGUAGE SUMMARY

Interventions for maintaining surgically included remission in Crohn's disease

What is the aim of this review?

The aim of this Cochrane Review was to find out which drugs are most effective for maintaining remission in people with Crohn's disease who have undergone surgery to achieve remission. We collected and analysed all relevant studies to answer this question. We examined these studies using a method known as network meta-analysis (NMA) in order to compare and rank all the treatments in terms of clinical relapse, endoscopic relapse and safety.

What was studied in the review?

Crohn's disease is a chronic disease of the gut. It is known to change from periods when people experience a flare-up of the disease (relapse) to periods of good health (remission). Symptoms include abdominal pain, diarrhoea and weight loss. People with Crohn's disease may undergo surgery to remove diseased parts of their gut and achieve remission. However, their symptoms return after a while. Different drugs can be given to ensure that people with Crohn's disease remain in remission for as long as possible. These drugs include mesalazine, antibiotics, corticosteroids, and adalimumab, amongst others. Whilst these drugs have been known to reduce inflammation (pain and swelling) in the gut, side effects can occur with their use. We attempted to find out which treatments are the safest and most effective for maintaining remission in people with Crohn's disease after surgery.

How up-to-date is the review?

We searched for studies published up to 15 January 2019.

What are the main results of the review?

We included 35 relevant trials, which were published between 1976 and 2018. The studies included a total of 3249 participants who were mostly adults. Our NMA included 26 studies (2581 participants) and compared nine groups of treatments such as 5-aminosalicylic acid, adalimumab, antibiotics, budesonide, infliximab, probiotics, purine analogues, sulfasalazine, and a combination of sulfasalazine and prednisolone, which are used in preventing relapse after surgery in people with Crohn's disease. Adalimumab may reduce the chance of clinical relapse compared with placebo (dummy treatment). 5-aminosalicylic acid probably reduces the chance of clinical relapse compared with placebo. Budesonide may not be effective in preventing clinical relapse. The entire network evidence is of low certainty due to the small number of participants included in the studies and high risk of bias. This means that are confidence in these results is limited. Research to understand the effect of the treatments on endoscopic relapse and safety was limited, however cases of pancreatitis and leukopenia were reported in participants who received purine analogues.

Key messages

We uncertain about which treatments are most effective in preventing postoperative relapse in Crohn's disease. Alhough there is limited research on the harms (side effects) of these treatments, there were reported instances of pancreatitis and leukopenia in participants who received purine analogues.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Estimates of effects, credible intervals, and certainty of the evidence for maintenance of surgically induced remission in Crohn's disease

Patient or population: surgically induced remission in Crohn's disease
Settings: hospital, home, or combination, range of follow-up between 3 and 36 months
Intervention: 5-ASA, adalimumab, antibiotics, budesonide, infliximab, probiotics, purine analogues, sulfasalazine, sulfasalazine + prednisolone
Comparison: placebo

Outcomes	Effects and confidence in the estimate of effects*					Certainty of evidence	Interpretation
	Adalimumab	Infliximab	Budesonide	5-ASA	Purine analogues		
Clinical relapse Follow-up: 3 to 36 months							
Placebo Comparator	HR 0.11 (0.02 to 0.33) Network estimate	HR 0.36 (0.02 to 1.74) Network estimate	HR 0.66 (0.27 to 1.34) Network estimate	HR 0.69 (0.53 to 0.87) Network estimate	HR 0.75 (0.55 to 1.00) Network estimate	⊕⊕◯◯ **low**[1,2] Certainty of evidence of the network	Effect estimates of the best 5 interventions have been presented
Rank 8 (6 to 10)	Rank** 1 (1 to 2)	Rank 2 (1 to 10)	Rank 3 (2 to 10)	Rank 4 (2 to 7)	Rank 5 (3 to 8)		
Endoscopic relapse Follow-up: 3 to 36 months							
Placebo Comparator	HR 0.10 (0.01 to 0.32) Network estimate	HR 0.24 (0.01 to 1.20) Network estimate	Not estimated	HR 1.22 (0.61 to 2.18) Network estimate	HR 0.85 (0.33 to 1.61) Network estimate	⊕⊕◯◯ **low**[1,2] Certainty of evidence of the network	Interventions reported here were chosen based on the intervention reported for clinical relapse
Rank 5 (3 to 7)	Rank 1 (1 to 2)	Rank 2 (1 to 6)	Not estimated	Rank 6 (3 to 7)	Rank 4 (4 to 7)		
Withdrawal due to adverse events Follow-up: 3 to 36 months							

Placebo Comparator	HR 11.74 (0.12 to 55.06)	HR6.37 (9.14E-04 to 21.74) Network estimate	HR 1.64 (0.17 to 6.19) Network estimate	HR 1.19 (0.39 to 3.14) Network estimate	HR 2.51 (0.79 to 7.35) Network estimate	⊕◯◯◯ **very low**[2,3] Certainty of evidence of the network	Interventions were chosen based on the interventions considered beneficial in terms of clinical relapse
Rank 4 (2 to 7)	7 (1 to 9)	Rank 2 (1 to 9)	Rank 4 (1 to 9)	Rank 4 (2 to 7)	Rank 7 (4 to 9)		

*Estimates are reported as hazard ratio (HR), credible interval. Results are expressed in credible intervals as opposed to confidence intervals as a Bayesian analysis has been conducted

**Median rank and credible intervals for efficacy outcome are presented. Rank statistics are defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on, effective treatment

5-ASA: 5-aminosalicylic acid

GRADE Working Group grades of evidence

High certainty: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: We are very uncertain about the estimate.

[1]Downgraded two levels: once for high risk of bias and once for imprecision.

[2]There was no significant intransitivity, with comparable distribution of plausible effect modifiers across trials of different interventions for maintenance of remission.

[3]Downgraded three levels: once for high risk of bias and twice for imprecision.

BACKGROUND

Description of the condition

Crohn's disease is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract. There is no cure for the disease, so management strategies are instead focused on induction and maintenance of remission, as well as supporting the many other symptoms that impact those affected by the condition.

Approximately 75% of people with Crohn's disease will eventually undergo surgical resection (Bernell 2000), with recent studies suggesting a rate of 3.8 operations per 100 person-years (Ma 2017), and this can induce remission. However, endoscopic recurrence of disease has been reported to be as high as 61% six months postsurgery (Orlando 2014), and clinical relapse rates have been reported to range from 20% to 86% at five years postsurgery (Gklavas 2017; Rutgeerts 2002).

Given these high relapse rates, many studies have attempted to identify potential methods of prolonging postoperative remission, but there is no standard therapy for the prevention of postoperative recurrence in Crohn's disease (Hanauer 2001; NICE 2012). A number of agents have been studied, but considerable uncertainty remains as to the efficacy of such treatments.

Description of the intervention

Corticosteroids, the mainstay of treatment of acute exacerbations, are not effective for maintenance of remission in Crohn's disease (Steinhart 2003), and chronic use is limited by numerous adverse events.

Probiotics and budesonide do not appear to provide any benefit for maintenance of surgically induced remission (Doherty 2009). Nitroimidazole antibiotics may reduce relapse after surgery, although this benefit did not remain significant on sensitivity analysis, and the antibiotics were not well tolerated and were associated with a higher risk of serious adverse events (Doherty 2009).

5-aminosalicylates are a group of compounds that have long been used in inflammatory bowel disease (IBD). The first 5-aminosalicylate agent used in clinical practice was sulfasalazine, which is composed of sulfapyridine linked by an azo bond to 5-aminosalicylic acid (5-ASA). Sulfasalazine was first used in the 1940s as a treatment for arthritis (Svartz 1942). Improvement in gastrointestinal symptoms was noted in patients who had concurrent ulcerative colitis, leading to further use of this agent in IBD. 5-aminosalicylic acid has been shown to be safe and may be effective for maintenance of postsurgical remission when compared with placebo (Gjuladin-Hellon 2019a).

Purine analogues, such as azathioprine (AZA) and 6-mercaptopurine (6-MP), have also been shown to be effective when compared with placebo (Gjuladin-Hellon 2019b). However, on review the majority of studies compared these agents with 5-ASA and failed to demonstrate superiority, with more issues leading to withdrawal of therapy noted (Gjuladin-Hellon 2019b). These reviews led the National Institute for Health and Care Excellence (NICE) in the UK to change their guidance for maintenance of postsurgical remission in Crohn's disease to include the option of 5-ASA agents (NICE 2012). Tumour necrosis factor-alpha (TNF-α) antagonists may provide a benefit in postoperative Crohn's disease (Doherty 2009; Gjuladin-Hellon 2019a), but issues of cost and safety exist (Di Sario 2016).

How the intervention might work

Corticosteroids, budesonide, and 5-ASA agents all act as anti-inflammatory agents. Azathioprine is a prodrug that is non-enzymatically degraded to 6-MP, which in turn is metabolised to the active component 6-thioguanine nucleotide (6-TGN). 6-thioguanine nucleotide is thought to work by inhibiting the proliferation of T and B lymphocytes and reducing the numbers of cytotoxic T cells and plasma cells. Some trial data suggest that neutrophil count is a predictor of induction and maintenance of remission in Crohn's disease (Colonna 1994), which may suggest the mechanism of action, although this is not well understood. The major limiting factor for the long-term use of AZA has been the occurrence of adverse events leading to withdrawal of therapy in approximately 10% of patients (Hafraoui 2002), with dose-dependent and idiosyncratic adverse events occurring. Tumour necrosis factor-alpha antagonists are monoclonal antibodies directed towards TNF-α. Although TNF-α antagonists have been the benchmark biologic therapies for more than a decade, the exact mechanism of action is still incompletely understood (Levin 2016). The mechanism by which probiotics and antibiotics may act is poorly understood. Due to the role that dysbiosis plays in IBD, it has been hypothesised that there is benefit in trying to restore the indigenous flora. Several observations, both in humans and animal models, emphasised the importance of bacterial flora in IBD pathogenesis, justifying the current interest in antibiotic and probiotic therapies aimed at the manipulation of enteric flora (Cui 2004).

Why it is important to do this review

Given the impact of surgical resection on Crohn's disease patients, clear evidence regarding management strategies to maintain a disease-free state postsurgically is vital for both patients and clinicians. Many researchers have argued that the state of the gut postsurgery is massively different from a histological and clinical standpoint (Gordon 2017), and previous reviews have found that some standard treatments work in this setting and some do not (Gjuladin-Hellon 2019a; Gjuladin-Hellon 2019b). With a wide range of strategies available and no clear hierarchy regarding the efficacy of these treatments, evidence-based decision making is currently not possible. Additionally, given the variability in ad-

verse event profiles and tolerability of the agents being considered, clarification of these issues was needed.

Comparative efficacy and safety data are best achieved by head-to-head trials. However, multiple trials of this sort will be needed, and attracting funding to complete these trials may be difficult and take significant time, if these trials are conducted at all. Thus far, there are limited active head-to-head trials comparing treatments for maintaining postsurgical remission in Crohn's disease. An alternative strategy for obtaining comparative data is to conduct a network meta-analysis (NMA) in which multiple treatments are compared using both direct comparisons of interventions within randomised controlled trials (RCTs) and indirect comparisons across trials based on a common comparator (i.e. placebo). In other words, if compound A is compared with compound B in one trial, and the same compound B is compared with compound C in another trial, indirect information can be obtained for the comparison of compound A to compound C using this technique. After publication of the protocol for this review (Clegg 2018), NICE in the UK convened a similar scoped update in this area which has now been published (NICE 2019). However, the NICE guideline is limited to studies that maintained remission for 12 months, unlike the portfolio of IBD maintenance Cochrane Reviews. The NICE guidelines also include studies that do not meet the transitivity assumptions of this Cochrane Review. These factors are bound to result in differences in conclusions. It is also key to recognise that the NICE guideline also includes cost as a key determinate of its recommendations. This will also lead to differences in conclusions between their findings and this review. It was therefore key to complete a Cochrane NMA in this area.

OBJECTIVES

To assess the effects and harms of interventions for the maintenance of surgically induced remission in Crohn's disease and rank the treatments in order of effectiveness.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of language or year of publication. We excluded studies that used quasi-random methods of allocation (e.g. date of birth).

Types of participants

We considered for inclusion trials enrolling participants of any age with Crohn's disease as defined by conventional clinical, radiological, or endoscopic criteria.

Participants had to be in remission as defined by a recognised Crohn's disease activity index or endoscopy following surgery on recruitment, or to have undergone a surgical resection (as defined by the authors of the primary studies) no more than six months prior to starting maintenance treatment. Studies that recruited participants in any sort of relapse (clinical, endoscopic, or histologic, etc.) were excluded (with the exception of Reinisch 2010, which included some participants with endoscopic recurrence). We only included studies with a mixed population (both medically and surgically induced remission) provided outcome data for participants with surgically induced remission were reported separately.

Types of interventions

We considered for inclusion trials comparing oral or topical corticosteroids, 5-ASA agents, purine analogues, TNF-α antagonists, other classes of biologic agents, probiotics, antibiotics, or any other pharmaceutical intervention with no treatment, placebo, or another active treatment. For studies to be included, participants had to have received therapy for a minimum period of three months. We included studies where participants received concomitant treatments that are not routinely administered for the purpose of maintaining remission (such as antidiarrhoeal medication, antibiotics, or tapered steroids). We did not include dose optimisation studies. Given the scope of overlapping and ongoing reviews, we did not consider trials assessing enteral diet, diet manipulation, herbal medicine, or nutritional supplementation. We used the term 'comparison' to mean two interventions compared in a single study, and the term 'contrast' to mean two interventions compared across all studies with that comparison. 'Combination treatments' involved two or more active treatments that are used in inducing or maintaining remission in people with Crohn's disease.

Types of outcome measures

Primary outcomes

The primary outcome was clinical relapse. We regarded the following as providing the most relevant measures of outcome for the analyses.

1) The proportion of participants who failed to maintain clinical remission, as defined by the original studies.

2) The time to relapse (survival data: study-level data reported as a hazard ratio (HR) with standard error (SE)).

We accepted the authors' definitions of what constitutes a clinical relapse.

Secondary outcomes

1) Endoscopic relapse, as defined by the original studies.
2) Histologic relapse, as defined by the original studies.
3) Adverse events (as defined by FDA 2018. We also noted where studies failed to provide sufficient information and simply reported outcome as 'adverse event').
4) Serious adverse events (as defined by FDA 2018. We also noted where studies failed to provide sufficient information and simply reported outcome as 'serious adverse event').
5) Withdrawal due to adverse events.
We reported outcome measures at the last time point available (assumed to be at the end of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this differed from the last time point available). However, we also indicated when studies reported outcomes at other time points.

Search methods for identification of studies

Electronic searching

We searched the following electronic databases from inception to January 2019 for relevant studies:

1. Cochrane IBD Group Specialized Register (to 31 January 2019)
2. CENTRAL (the Cochrane Library 2018, Issue 1);
3. MEDLINE (1946 to 31 January 2019);
4. Embase (1980 to 31 January 2019);
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/); and
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

The search strategy was not limited by language (see Appendix 1).

Reference searching

We inspected the references of all identified studies and relevant systematic reviews for additional trials.

Abstracts of major gastroenterology meetings

We performed a manual search of abstracts submitted to major gastroenterology meetings (2015 to 2018) for the following journals in order to identify trials that may have not been published in full at the time of the review:

1. *Gastroenterology* (American Gastroenterological Association);
2. *Gut* (British Society of Gastroenterology);
3. *American Journal of Gastroenterology* (American College of Gastroenterology);
4. *Canadian Journal of Gastroenterology* (Canadian Association of Gastroenterology);
5. *Journal of Pediatric Gastroenterology and Nutrition* (European Society for Paediatric Gastroenterology, Hepatology and Nutrition); and
6. *Journal of Pediatric Gastroenterology and Nutrition* (North American Society of Pediatric Gastroenterology, Hepatology and Nutrition).

Personal contacts

We contacted leaders in the field (Hans Herfarth) in an attempt to identify additional studies, but received no reply.

Drug companies

We contacted Danone for additional data.

Data collection and analysis

We carried out data collection and analysis according to methods stated in the published protocol (Clegg 2018), which were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors independently screened the titles and abstracts of studies located by the search and identified potentially relevant papers, which were retrieved in full text. The review authors independently assessed the eligibility of the full texts using the above-mentioned inclusion criteria. Any disagreements were resolved by discussion and consensus or by consulting a third review author if necessary. We contacted study authors for clarification regarding study eligibility where required. Studies with multiple publications were included only once, however we extracted relevant data from all the reports.

Data extraction and management

We developed a data extraction form that we used to extract information on relevant features and results of included studies. Two review authors independently extracted and recorded data on the predefined checklist. We extracted data on the following items:

- characteristics of participants: age, sex, disease distribution, disease duration, disease activity index;
- total number of participants originally assigned to each treatment group;
- intervention: type and dose of agent;
- control: placebo, other drugs;
- concurrent medications; and
- outcomes: time of assessment, length of follow-up, type of Crohn's disease activity index (CDAI) used, definitions of remission and relapse, site of surgery, relapse rates, adverse events.

Assessment of risk of bias in included studies

Two review authors independently assessed bias using the Cochrane 'Risk of bias' tool (Higgins 2011). We assessed the following study features:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- completeness of outcome data;
- selective reporting; and
- other sources of bias.

We rated each of these factors as low, high, or unclear risk of bias. After carrying out 'Risk of bias' assessment at study level, we then used the CINeMA (Confidence in Network Meta-Analysis) web tool to calculate the percentage contribution of each direct contrast to each network estimate (CINeMA 2017). We also calculated the overall risk of bias for in the entire network. In addition, we produced an all-domain risk of bias for each study as shown in Norman 2018 by assigning four ratings: low, unclear, high and very high. The four ratings were defined as:

- 'very high' - two or more key domains with a high risk of bias or a single domain with very high levels of uncertainty
- 'high' - high risk of bias for any one domain;
- 'low' - low risk of bias for each of the key domains;
- 'unclear' - low risk of bias in all but one domain with insufficient information.

We included it in the risk of bias table for each study.

Measures of treatment effect

We calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI) for dichotomous outcomes using a random-effects model. We intended to calculate the mean difference (MD) and corresponding 95% CI for continuous outcomes measured using the same units, and standardised mean differences (SMD) with corresponding 95% CI for continuous outcomes where different scales were used to evaluate the same outcome. We interpreted SMDs according to Cohen 1988: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect. The treatment effects of pairwise comparisons were summarised using RR estimates and associated two-sided 95% CIs. Hazard ratios (HRs) and 95% credible intervals (95% CrIs) were calculated for the NMA. Effect estimates and credible intervals with a high number of zeros were reported as exponents. For example 0.0000345 = 3.45E-05; 345000 = 3.45E+05.

Unit of analysis issues

Given the nature of the interventions, we assumed that only simple parallel-group design trials would be available, with no cluster-randomised trials. If cluster-randomised trials are identified in future updates, these will be included and, if unit of analysis issues are identified (e.g. randomisation and analysis at different units), the sample sizes or standard errors will be adjusted appropriately (Higgins 2011). Where cross-over trials become available in future, these will be included, and the effect estimates from the first period prior to cross-over included in the meta-analysis. Where outcomes were reported at several time points, analyses were undertaken at the single time point that was consistently reported by the trials and at the longest point of follow-up. For our NMA, we ensured that the effects of correlated effect estimates were accounted for using appropriate methods (see Data synthesis).

Dealing with missing data

Where dichotomous outcome data were missing, we used the intention-to-treat principle (ITT) on the assumption that all participants lost to follow-up were treatment failures. We considered this approach appropriate for the clinical and endoscopic relapse outcomes.

Assessment of heterogeneity

We assessed heterogeneity and inconsistency to ensure the validity of the analysis. We initially assessed heterogeneity through visual inspection of forest plots and the calculation of the Chi^2 and I^2 statistics (Borenstein 2009). For the NMA, we intended to use the between-study standard deviation to assess heterogeneity, with a threshold of 0.5 indicating heterogeneity (Higgins 2011). We assessed consistency within the analysis through comparison of the estimates of treatment effect for each comparison from the direct and indirect pairwise meta-analyses for the closed loops within the NMA, using a node-splitting approach (Cooper 2009; Dias 2010). It is important that the direct and indirect evidence for the same comparisons agree, as joint analysis on an inconsistent network can be misleading. Possible explanations for heterogeneity were to be examined where sufficient data were available, including factors such as participant characteristics (e.g. age, sex), condition severity, treatment type and dose, healthcare system, and country. Where appropriate, these factors would have been investigated further through subgroup analyses and meta-regression (Borenstein 2009). We explored possible causes of methodological heterogeneity through sensitivity analyses where sufficient data were available (Sutton 2000). This included assessing the effects of studies that may be affected by such factors as risk of bias associated with allocation concealment, high loss to follow-up, or lack of blinding in assessment of outcomes.

Assessment of reporting biases

We investigated potential publication bias using funnel plots (trial effects versus trial size). We also scrutinised studies to assess the impact of funding bias and small-study effect.

Data synthesis

We synthesised the studies through a narrative review with tabulation of results of included studies. Where possible, we further synthesised treatment effects for all comparisons and outcomes through meta-analyses, with the approach taken dependent on the outcome assessed and the data available (Borenstein 2009). Where the outcomes represented time-to-event data (e.g. time to relapse), the (log) HR with 95% CI or 95% CrI was used as the summary measure, adopting the approaches suggested by Sutton and colleagues given the available data (Egger 2001; Parmar 1998; Sutton 2000).

Different approaches were taken for the meta-analysis. Firstly, direct comparisons of treatment effects were conducted through pairwise meta-analyses. Secondly, the opportunity for estimating an NMA was assessed to compare different interventions through both direct and indirect evidence within connected networks of trials (Spiegelhalter 2004; Welton 2012). Only studies that met the transitivity assumption were included in the NMA. Transitivity is an assumption that an intervention effect for a direct comparison will be equivalent to the same intervention effect for an indirect comparison. Trials that offered participants non-randomised active treatments did not meet the transitivity assumption and were not included in the NMA. The use of direct and indirect evidence can strengthen inferences about the relative efficacy of the interventions being compared, whether due to a lack of, or sparse, evidence comparing the different interventions. Importantly, NMAs allow for the comparison of multiple interventions simultaneously and for an estimation of the rank order based on efficacy (Welton 2012). The network for the models was presented graphically through network diagrams, allowing assessment of both the structure and extent of the evidence available for the different comparisons. Where heterogeneity was identified, its possible causes were to be investigated through the inclusion of participant and study level characteristics as covariate within meta-regression analyses. The meta-regression included factors such as baseline risk (surrogate measure of participant characteristics) and length of follow-up (Gjuladin-Hellon 2019a; Gjuladin-Hellon 2019b), adopting the approach outlined by Achana and colleagues (Achana 2013). Where multiple active treatment arms of the same class of drug or different doses of the same drug are included, comparisons may be correlated, influencing the outcome measure. Such correlations were accounted for by assuming that the treatment effects from multi-arm studies were from a multivariate normal distribution, decomposing it into a series of conditional univariate distributions (Warren 2014). Some interventions were considered sufficiently similar to have a 'class effect', with meta-analyses 'lumping' these interventions together. Aminosalicylates were split into two separate interventions: sulfasalazine and 5-ASA (e.g. mesalazine, etc.), whilst azathioprine and 6-MP were lumped together. As pooling treatments that may be heterogeneous does not meet the consistency assumption, with the potential to cause conflict between the direct and indirect evidence, NMAs for the individual and classes of interventions were estimated where evidence allowed, and the estimates compared (Welton 2012). Where interventions routinely used for maintaining remission are administered as concomitant treatments, such studies were excluded from the network.

All NMAs took a Bayesian approach through Markov Chain Monte Carlo (MCMC) simulation. The parameters considered in the models were the treatment effect of an intervention compared with other interventions, with the likelihood function dependent on the outcome used. As the primary outcome (i.e. clinical relapse) represents the number of events that occur within a patient population allocated to a particular treatment, a binomial distribution was assumed for the likelihood and a clog-log link was used for the linear predictor to take time into account. Trial specific log-HRs were assumed to be from the normal distribution. Different prior distributions were to be used for the scale parameters (e.g. a uniform distribution for the base case and half-normal and inverse gamma distributions for sensitivity analyses). Vague priors were used for the treatment effects in the different models. All models were estimated using two chains starting with different initial values. Convergence was assessed through visual inspection of the Brooks-Gelman-Rubin diagnostic, with convergence assumed to have occurred when the ratio of between- and within-chain variability was stable around one. Varying iterations and burn-in periods were used to ensure convergence, with burn-in periods discarded from the analysis. Autocorrelation plots were examined, with different rates of thinning applied to eliminate or reduce its effects where present. We ran all the models based on 100,000 iterations for 2 independent chains after a burn-in of 100,000.

Adequacy of the fit of the models was assessed through a comparison of the residual deviance for the models with the number of unconstrained data points available, with an adequate fit when both closely matched. Model selection and overall goodness of fit were assessed through deviance information criteria (DIC), with a threshold of a difference of three to five points considered significant (lowest DIC most appropriate fit) (Spiegelhalter 2002; Welton 2012). The adequacy of the approach used for the NMA was meant to be assessed using a standard critical appraisal tool (Jansen 2014). Where the threshold of difference was not met, we used the random-effects model to obtain a more conservative interpretation.

We conducted pairwise meta-analyses of direct comparisons using RevMan 5 Version 5.3. (Review Manager 2014) and Stata 2017 software (Stata 2017; Egger 2001; Higgins 2011), whilst NMAs were estimated using the WinBUGS software (version 1.4.3) (MRC Biostatistics Unit, Cambridge, UK) (Lunn 2000).

Subgroup analysis and investigation of heterogeneity

As previously noted, where heterogeneity was identified its possible causes were to be investigated through the inclusion of participant and study level characteristics as covariates within a meta-regres-

sion analysis. The meta-regression was to include factors such as baseline risk (surrogate measure of participant characteristics) and length of follow-up (Gjuladin-Hellon 2019a; Gjuladin-Hellon 2019b), adopting the approach outlined by Achana 2013. We did not perform meta-regression due to the small number of trials informing the direct comparisons within the network.

Assessment of statistical heterogeneity

We used the I^2 statistic to carry out a statistical assessment of the disagreement between estimates within each pairwise comparison (Higgins 2011). We also visually assessed the overlap of the confidence intervals and the variability in the point estimates. We interpreted I^2 thresholds as follows.

- < 50%: low
- 50 to 75%: moderate
- > 75%: large

Assessment of statistical inconsistency

We also assessed whether there were any disagreements between direct and indirect estimates or between indirect estimates through different intermediate treatments in the network. This was done for single loops of evidence within the network and for the network as a whole (Dias 2010; Salanti 2014).

Local approaches to evaluating inconsistency

The first stage involved separately synthesising the evidence for each pairwise contrast. This method tested the consistency assumption for each closed loop of the network separately, then the magnitude of the inconsistency factors and their confidence intervals were used to make inferences about the presence of inconsistency in each loop. This was followed by the node-splitting approach to compare direct and indirect relative treatment effects. For instance, a direct estimate of C versus B is compared with the indirect estimate from AB versus AC (Dias 2010). A test of the null hypothesis that there is no inconsistency is obtained using a Z-test. One test was carried out for each treatment comparison. The ratio of odds ratios with confidence interval was calculated each time. A confidence interval excluding 1 indicated statistically significant inconsistency. These were automated in the CINeMA web tool.

Global approaches to evaluating inconsistency

Using the CINeMA web tool, we also conducted a global assessment of inconsistency in the network using a Chi^2 test. This was useful in assessing whether the assumption of consistency holds for the entire network. Treatment comparisons that take ≥ 90% of the information from direct evidence are unlikely to be of concern for inconsistency. For comparisons with at least 10% of information derived from indirect evidence, a P value < 0.01, 0.01 to < 0.1, and > 0.1 was interpreted as major, some, and no concerns, respectively. Given that the CINeMA web tool had not been fully adapted for the Bayesian framework at the time of preparing this review, we made adjustments to some interpretations that were not consistent with the results obtained from WinBUGS.

Investigation of heterogeneity and inconsistency

If sufficient data become available in future updates of this review, we will perform subgroup analyses assessing the effect of time since surgery (≤ 30 days versus > 30 days) and type of remission (clinical versus endoscopic at the point of recruitment) on the outcomes. We also planned a subgroup analysis on duration of follow-up, however this was no longer deemed necessary as the clog-log link in the simulation models was designed to take time into consideration (Data synthesis).

Sensitivity analysis

We examined methodological heterogeneity through sensitivity analysis, including such components of risk of bias as allocation concealment, loss to follow-up, or blinding of outcome assessment. We also excluded studies that were outliers in terms of dose of intervention, definition of outcome, direction or size of treatment effect, or those identified as inconsistent by inconsistency testing.

Quality assessment of evidence generated from the network meta-analysis

We assessed the certainty of the evidence using GRADE (Schünemann 2011a; Schünemann 2011b). We applied this methodology to the NMA by focusing on the approach of Salanti 2014. This was carried out using GRADEpro GDT (GRADEpro 2015) and the CINeMA web tool where possible (CINeMA 2017). The CINeMA web tool assesses NMA evidence based on the five GRADE domains listed below, and downgrades pairwise, mixed, and indirect evidence depending on whether there are major, some, or no concerns. We assessed the quality of the evidence in two main ways: firstly, for each contrast, and secondly, for the network as a whole, in order to assess the quality of the ranking order. We assessed individual GRADE factors as follows.

- Risk of bias: we assessed overall risk of bias for each contrast and also for the entire network.
- Indirectness: this relates to whether the population, intervention, and outcome in the studies differ from those we have proposed (see Criteria for considering studies for this review) as well as intransitivity.
- Inconsistency: at the level of the contrast, we considered both heterogeneity in the direct evidence for that comparison and inconsistency related to different routes of analysis for the comparison (e.g. direct versus indirect evidence and two-arm versus three-arm trials). The latter was conducted using a node-splitting approach (Dias 2010). As well as assessing the meta-analyses of the direct evidence for inconsistency, we considered

the NMA predictive intervals for that comparison in relation to GRADE 'default' minimum important differences (0.75 and 1.25) (Guyatt 2011), using CINeMA. We note that inconsistency can only be assessed where there is both direct and indirect evidence. We assessed GRADE inconsistency as serious limitations if there was heterogeneity in the direct estimate or inconsistency in the network with respect to that comparison. We assessed the comparison as having very serious limitations if there was severe heterogeneity or severe inconsistency or limitations with both heterogeneity and inconsistency. The review authors arrived at judgements on the magnitude of limitations through discussion. Rationales were described transparently in the review report. At the level of the network, we relied on the DIC estimate of the inconsistency model. Additionally, if several contrasts showed direct and indirect results that would have led to different clinical decisions, we considered inconsistency to be present.

- Imprecision: at the level of the contrast, we assessed imprecision for each pairwise comparison using the GRADE default minimally important difference values of 1.25 and 0.75 for the OR. We also took into account the sample size for the direct evidence informing this contrast, and considered it in relation to the optimal information size.
- Publication bias: was also assessed for each pairwise comparison using standard GRADE; we used the contributions matrix to translate these judgements to the network as a whole.

'Summary of findings' table

We presented the main results on clinical relapse, endoscopic relapse, and withdrawal due to adverse events in 'Summary of findings' tables, reporting the results for a representative set of contrasts, with one row for each intervention versus the reference comparator. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data (Schünemann 2011a). 'Summary of findings' tables also include an overall grading of the evidence using the GRADE approach. We adopted a modified version of the new 'Summary of findings' tables format for NMAs (Yepes-Nuñez 2019).

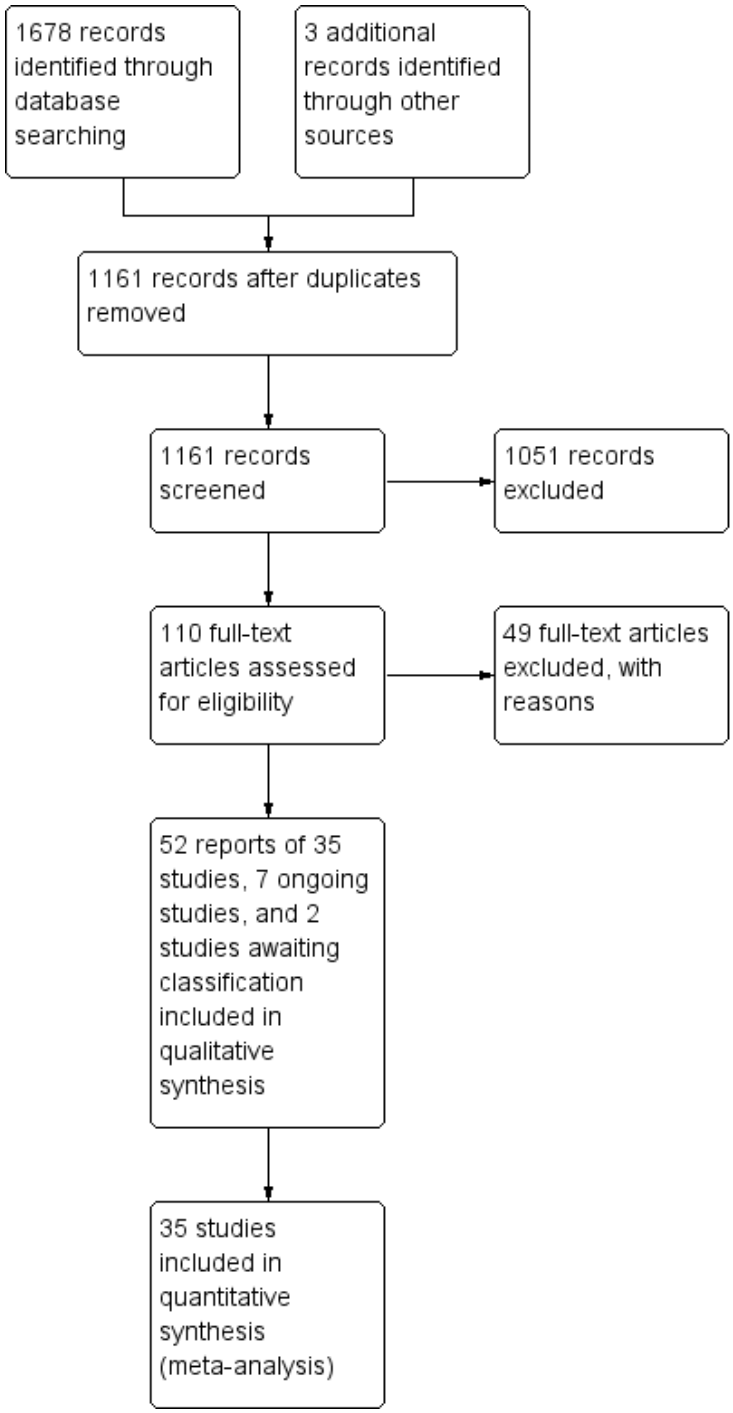
RESULTS

Description of studies

Results of the search

The literature search identified a total of 1678 records through database searching. A total of three additional records were identified from other sources. After removal of duplicates 1161 unique records remained. Examination of the titles and abstracts found 110 records for full-text screening. After assessing the full texts of 110 records, we identified 52 reports of 35 studies, 7 ongoing studies, and 2 studies awaiting classification that met the inclusion criteria and were included in the review. We excluded 49 records for various reasons. The results of the search are presented in the PRISMA flow diagram (Figure 1). Detailed information about these studies is presented in the Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables, and summarised below.

Figure 1. Study flow diagram.



Included studies

Study design and setting

The included studies were RCTs published between 1976 and 2018. The single-centre RCTs were conducted in Italy (Ardizzone 2004; Armuzzi 2013; Prantera 2002; Savarino 2013; Tursi 2014), the USA (Regueiro 2009, Israel (Scapa 2015), and Japan (Yoshida 2012). The multicentre studies were conducted in different locations in the following countries: Germany (Ewe 1989; Ewe 1999), Belgium (D'Haens 2008; Gossum 2007; Rutgeerts 2005), Canada (Fedorak 2015; McLeod 1995), Spain (Lopez Sanroman 2017; Mañosa 2013), the UK (Mowat 2016), Italy (Brignola 1995; Caprilli 1994; Caprilli 2003), Israel (Chermesh 2007), the USA (Herfarth 2013), and Japan (Fukushima 2018); or as a multinational collaboration of several countries across Europe (Fedorak 2015; Hellers 1999; Lochs 2000; Marteau 2006; Reinisch 2010), Europe and the USA (Hanauer 2004), or Europe, Canada, Australia, and the USA (Regueiro 2016). The trials were conducted in gastroenterology hospitals and medical clinics or centres, Chermesh 2007; Ewe 1989; Ewe 1999; Florent 1996; Lochs 2000; Lopez Sanroman 2017; Marteau 2006; Reinisch 2010; Sutherland 1997; Wenckert 1978, or through a collaboration between university clinics and hospitals or medical centres, Ardizzone 2004; Bergman 1976; Brignola 1995; Caprilli 1994; Caprilli 2003; D'Haens 2008; Fedorak 2015; Fukushima 2018; Gossum 2007; Hanauer 2004; Hellers 1999; Herfarth 2013; Lochs 2000; Mañosa 2013; McLeod 1995; Regueiro 2009; Regueiro 2016; Rutgeerts 2005; Savarino 2013; Tursi 2014; Yoshida 2012, and secondary and tertiary hospitals (Mowat 2016). In four studies the care setting was unclear (Armuzzi 2013; Herfarth 2006; Prantera 2002; Scapa 2015).

Participants

The 35 included studies involved a total of 3249 participants, with sample sizes ranging between 20, in Tursi 2014, and 324, in Lochs 2000. The majority of the studies recruited participants within three months of surgery or before hospital discharge, except in Reinisch 2010, where participants were enrolled between 6 and 24 months' postsurgery. The time since operation was not reported in two studies (Mañosa 2013; Sutherland 1997). Investigations were carried out before disease activity was established through generally accepted endoscopic, histological, and/or radiological criteria. However, it is important to note that Reinisch 2010 included participants in subsequent postoperative clinical remission (CDAI < 200), but with signs of moderate to severe endoscopic recurrence. The average age of study participants was between 33.6 years, in Lochs 2000, and 38.8 years, in D'Haens 2008. In 11 studies participant age was reported as a median (Armuzzi 2013; Bergman 1976; Ewe 1989; Herfarth 2013; Lopez Sanroman 2017; Marteau 2006; Regueiro 2009; Rutgeerts 2005; Savarino 2013; Scapa 2015; Wenckert 1978). All studies were conducted in male and female adults except for three studies (Fedorak 2015; Hellers 1999; Mowat 2016), which based on inclusion criteria appear to have included people who were 16 years and older. None of the studies were conducted on paediatric participants alone.

The use of concomitant treatments was reported in 22 studies. Twenty studies prohibited the use of any Crohn's disease therapy other than the study intervention. Seven of these studies used corticosteroids (Armuzzi 2013; Ewe 1999; Hanauer 2004; Hellers 1999; Lochs 2000; Mañosa 2013; Rutgeerts 2005), which had to be gradually tapered within two to six weeks after surgery. In two studies metronidazole was administered to both intervention arms for the first three months (D'Haens 2008; Lopez Sanroman 2017). Mesalazine as concomitant treatment was administered to both intervention arms for the whole duration of the trial in Yoshida 2012. Two studies permitted the use of concomitant immunomodulators and mesalazine amongst participants who had had these drugs prescribed before surgery as long as the medication dose had been stable 12 weeks before surgery and remained so for the duration of the study (Regueiro 2009; Regueiro 2016). In Tursi 2014 both intervention arms received oral mesalazine for two weeks after surgery. The use of antidiarrhoeal drugs was reported in five studies (Ardizzone 2004; Caprilli 2003; Fedorak 2015; Hellers 1999; Lochs 2000). D'Haens 2008 permitted the use of topical therapy for perianal disease and colestyramine for the treatment of bile-acid diarrhoea. Continous use of non-steroidal anti-inflammatory drugs was prohibited, and only occasional use of paracetamol and tramadol was allowed in Savarino 2013. In Mowat 2016 any concomitant medications used were documented, and there was no reported use of an active concomitant treatment. In the rest of the studies concomitant treatments were not discussed (Bergman 1976; Brignola 1995; Caprilli 1994; Chermesh 2007; Ewe 1989; Herfarth 2006; Herfarth 2013; McLeod 1995; Prantera 2002; Scapa 2015; Wenckert 1978).

Interventions

All included studies were two-arm RCTs except for Hanauer 2004 and Savarino 2013, both of which had three intervention arms. Comparisons were made between oral or topical corticosteroids, immunosuppressants, aminosalicylates, TNF-α antagonists, probiotics, synbiotics and antibiotics or a combination of these treatments, with no treatment, placebo or another active treatment. Information on interventions and concomitant treatments was tabulated (Table 1) and is detailed below.

Active intervention versus no treatment

- 5-ASA versus no treatment (Caprilli 1994)
- TNF-α antagonists versus no treatment (Fukushima 2018)
- Prednisolone and sulfasalazine combined versus no treatment (Bergman 1976)

Active interventions versus placebo

- 5-ASA versus placebo (Brignola 1995; Ewe 1989; Florent 1996; Hanauer 2004; Lochs 2000; McLeod 1995; Sutherland 1997; Wenckert 1978)
- Immunusuppressants versus placebo (D'Haens 2008; Hanauer 2004; Mowat 2016)
- Budesonide versus placebo (Ewe 1999; Hellers 1999)
- Antibiotics versus placebo (Herfarth 2013; Mañosa 2013; Rutgeerts 2005)
- TNF-α antagonists + immunosuppressants + 5-ASA versus placebo + immunosuppressants + 5-ASA (Regueiro 2009; Regueiro 2016)
- Functional foods (probiotics/synbiotics) versus placebo (Chermesh 2007; Fedorak 2015; Gossum 2007; Marteau 2006; Prantera 2002)

Active treatment versus active treatment

- 5-ASA versus immunosuppressants (Ardizzone 2004; Hanauer 2004; Herfarth 2006; Reinisch 2010; Savarino 2013)
- 5-ASAs versus anti-TNF (Savarino 2013)
- High-dose 5-ASA versus low-dose 5-ASA (Caprilli 2003)
- TNF-α antagonists versus immunosuppressants (Armuzzi 2013; Lopez Sanroman 2017; Savarino 2013; Scapa 2015)
- TNF-α antagonists versus TNF-α antagonists (Tursi 2014)
- TNF-α antagonists + 5-ASA versus 5-ASA (Yoshida 2012)

Outcomes

Participants were followed up for a duration of three, Fedorak 2015; Florent 1996; Gossum 2007, to 72 months, McLeod 1995, or until relapse. During the study period, outcomes were collected and reported at multiple time points in 14 studies (Bergman 1976; D'Haens 2008; Ewe 1989; Ewe 1999; Florent 1996; Fukushima 2018; Lochs 2000; Mañosa 2013; McLeod 1995; Mowat 2016; Regueiro 2016; Rutgeerts 2005; Wenckert 1978; Yoshida 2012), and at a single time point in the remaining the studies. We disregarded any follow-up data collected after the studies were completed (i.e. post-therapy). Information on outcomes reported and definitions of key outcomes are summarised in Table 2 and also listed below.

Outcomes of interest reported in each included study are as follows.

- Total number of relapsed (a combination of different types of relapse) participants was reported in five studies (Bergman 1976; Caprilli 1994; Ewe 1989; Fukushima 2018; McLeod 1995).
- Clinical relapse was reported in 27 studies (Ardizzone 2004; Armuzzi 2013; Brignola 1995; Caprilli 2003; Chermesh 2007; D'Haens 2008; Ewe 1999; Fukushima 2018; Gossum 2007; Hanauer 2004; Herfarth 2006; Herfarth 2013; Lochs 2000; Lopez Sanroman 2017; Mañosa 2013; Marteau 2006; Mowat 2016; Prantera 2002; Regueiro 2009; Regueiro 2016; Reinisch 2010; Rutgeerts 2005; Savarino 2013; Sutherland 1997; Tursi 2014; Wenckert 1978; Yoshida 2012).
- Endoscopic relapse was reported in 27 studies (Armuzzi 2013; Brignola 1995; Caprilli 2003; Chermesh 2007; D'Haens 2008; Ewe 1999; Fedorak 2015; Florent 1996; Fukushima 2018; Gossum 2007; Hanauer 2004; Herfarth 2013; Lochs 2000; Lopez Sanroman 2017; Mañosa 2013; Marteau 2006; McLeod 1995; Mowat 2016; Prantera 2002; Regueiro 2009; Regueiro 2016; Reinisch 2010; Rutgeerts 2005; Savarino 2013; Scapa 2015; Tursi 2014; Yoshida 2012).
- Adverse events were reported in 24 studies (Ardizzone 2004; Brignola 1995; Caprilli 1994; Caprilli 2003; D'Haens 2008; Ewe 1999; Fedorak 2015; Florent 1996; Gossum 2007; Hanauer 2004; Hellers 1999; Herfarth 2013; Lochs 2000; Lopez Sanroman 2017; Mañosa 2013; Marteau 2006; McLeod 1995; Prantera 2002; Regueiro 2009; Regueiro 2016; Reinisch 2010; Rutgeerts 2005; Savarino 2013; Sutherland 1997).
- Serious adverse events were reported in 11 studies (Ardizzone 2004; Ewe 1999; Gossum 2007; Hanauer 2004; Hellers 1999; Lochs 2000; Lopez Sanroman 2017; Mañosa 2013; McLeod 1995; Reinisch 2010).
- Withdrawal due to adverse events was reported in 28 studies (Ardizzone 2004; Armuzzi 2013; Brignola 1995; Caprilli 1994; Caprilli 2003; D'Haens 2008; Ewe 1999; Fedorak 2015; Florent 1996; Gossum 2007; Hanauer 2004; Hellers 1999; Herfarth 2006; Herfarth 2013; Lopez Sanroman 2017; Mañosa 2013; Marteau 2006; McLeod 1995; Mowat 2016; Prantera 2002; Regueiro 2009; Regueiro 2016; Reinisch 2010; Rutgeerts 2005; Savarino 2013; Sutherland 1997; Tursi 2014; Wenckert 1978; Yoshida 2012).

Funding and declaration of interest

About 40% of the included studies failed to report any information regarding funding source and declarations of interest (Ardizzone 2004; Brignola 1995; D'Haens 2008; Ewe 1989; Ewe 1999; Fedorak 2015; Hellers 1999; Lochs 2000; Mañosa 2013; McLeod 1995; Prantera 2002; Regueiro 2009; Rutgeerts 2005; Scapa 2015; Yoshida 2012). Only nine studies provided information on both (Chermesh 2007; Fukushima 2018; Hanauer 2004; Lopez Sanroman 2017; Marteau 2006; Mowat 2016; Regueiro 2016; Reinisch 2010; Savarino 2013. Two studies declared conflicts of interest alone (Armuzzi 2013; Tursi 2014), whilst seven studies declared funding sources only (Bergman 1976; Caprilli

1994; Caprilli 2003; Florent 1996; Gossum 2007; Herfarth 2006; Herfarth 2013).

Of the studies that reported a declaration of interest, the authors declared there were no conflicts of interest in five studies (Chermesh 2007; Hanauer 2004; Mowat 2016; Savarino 2013; Tursi 2014). In the remaining studies, the authors declared educational or research grants, consultant or lecture fees or speakers honoraria.

Six studies were funded by pharmaceutical companies (Caprilli 1994; Caprilli 2003; Florent 1996; Herfarth 2006; Regueiro 2016; Reinisch 2010); two studies were funded by food companies (Gossum 2007; Marteau 2006); five studies received governmental grants (Bergman 1976; Fukushima 2018; Herfarth 2013; Lopez Sanroman 2017; Mowat 2016); and three studies reported that no grants had been received.

Excluded studies

We excluded 49 records for various reasons. The reasons for exclusion of each study are presented in the Characteristics of excluded studies table and are summarised below.

- Not an RCT (Armuzzi 2013; Angelberger 2013; Balzola 2010; Bodini 2014a; Bodini 2015; Bourreille 2005; Doherty 2009; Dumois 2001; Ewe 1980; Ewe 1981; Ford 2010; Herfarth 2014; Kennedy 2015; Manship 2015; Mardini 2005; McLeod 1997; Papamichael 2012; Regueiro 2013; Regueiro 2014; Reibetanz 2015; Sandborn 2004; Steinhart 1992; Yamamoto 2009; Yamamoto 2013)
- Wrong study design (De Cruz 2012; Kamm 2014a; De Cruz 2013b; De Cruz 2013c; De Cruz 2015a; De Cruz 2015b)
- Wrong intervention (Ferrante 2014; Kamm 2014b; Liao 2009; NCT00074542; NCT02247258; NCT02255370; Ren 2013; Tao 2009; Wright 2014; Wright 2015; Zhu 2015)
- Duplicate (De Cruz 2013a; NCT01190839; Vera-Mendoza 2017)
- Terminated (NCT01696942; NCT02247258; NCT02997059)
- Preliminary results of an included study (Ewe 1976; Ewe 1984)

Risk of bias in included studies

We assessed methodological rigour using the Cochrane 'Risk of bias' tool (Higgins 2011). Details of the 'Risk of bias' assessment for each study are presented in Characteristics of included studies, Figure 2, and Figure 3, and are summarised below.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

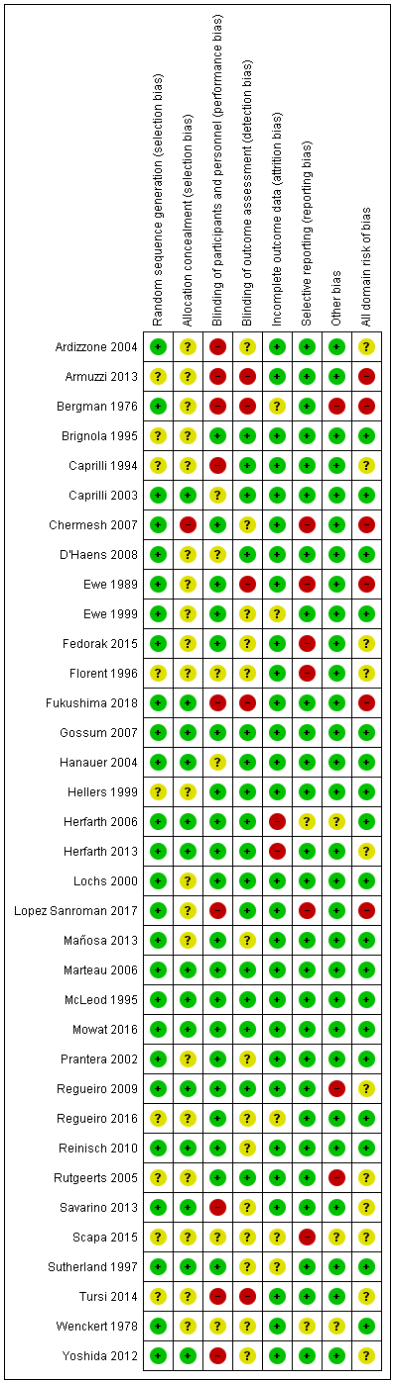
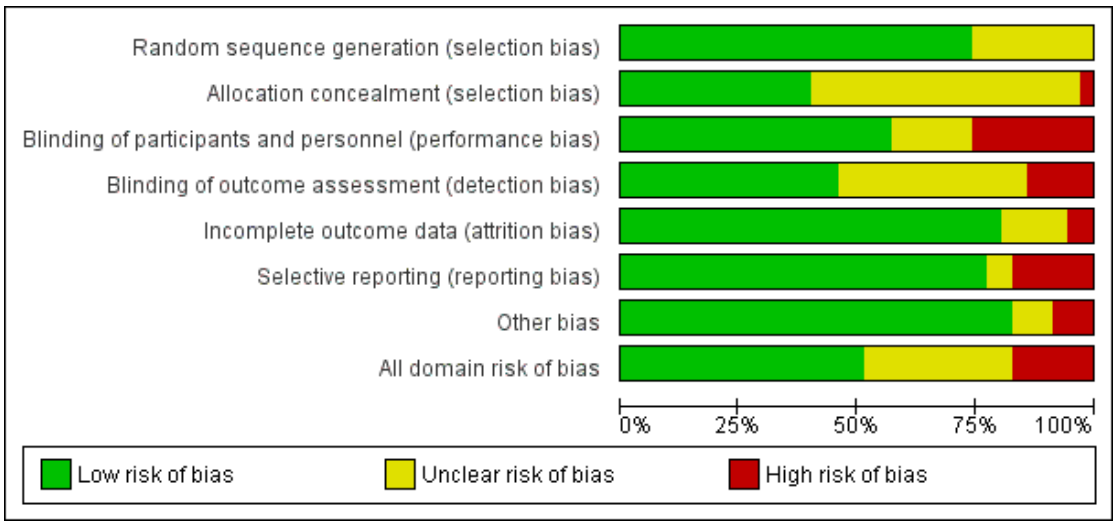


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

The method of participant allocation to study groups was described as 'random' in all of the included studies. Twenty-six studies provided sufficient information on random sequence generation and were judged as being at low risk of bias. We were unable to clarify the method of randomisation in nine studies, leading to a judgement of unclear risk of bias (Armuzzi 2013; Brignola 1995; Caprilli 1994; Florent 1996; Hellers 1999; Regueiro 2016; Rutgeerts 2005; Scapa 2015; Tursi 2014).

Allocation concealment

Thirteen studies were found to have adequate allocation concealment and were judged as at low risk of bias (Caprilli 2003; Fukushima 2018; Gossum 2007; Hanauer 2004; Herfarth 2006; Herfarth 2013; Marteau 2006; Mowat 2016; Regueiro 2009; Reinisch 2010; Savarino 2013; Sutherland 1997; Yoshida 2012). Twenty-two studies provided insufficient information to permit a judgement. We contacted the authors of these studies for clarification on allocation concealment, but received only one response. This was from Dr McLeod, who confirmed that McLeod 1995 had adequate allocation concealment, resulting in an assessment of low risk of bias. The rest of the studies were assessed as having inadequate description for allocation concealment and were marked 'unclear' (Ardizzone 2004; Armuzzi 2013; Bergman 1976; Brignola 1995; Caprilli 1994; D'Haens 2008; Ewe 1989; Ewe 1999; Fedorak 2015; Florent 1996; Hellers 1999; Lochs 2000; Lopez Sanroman 2017; Mañosa 2013; Prantera 2002; Regueiro 2016; Rutgeerts 2005; Scapa 2015; Tursi 2014; Wenckert 1978). Upon contact, the authors of Chermesh 2007 indicated that the allocation was performed using a predefined note for each participant. We did not consider this sufficient to prevent bias, therefore we assessed this study as at high risk of bias.

Blinding

Blinding of participants and personnel

We assessed nine studies as being at high risk of bias (Ardizzone 2004; Armuzzi 2013; Bergman 1976; Caprilli 1994; Fukushima 2018; Lopez Sanroman 2017; Savarino 2013; Tursi 2014; Yoshida 2012). These studies were all open-label trials, except for Bergman 1976, which albeit providing insufficient information, was judged to be at high risk of bias due to review authors' doubts about the feasibility of blinding participants and personnel in a non-placebo

trial (i.e. active treatment versus no treatment control). Approximately 57% of the studies gave an adequate description of the blinding method and were judged as at low risk of performance bias. The method of blinding was not adequately described in six studies (Caprilli 2003; D'Haens 2008; Florent 1996; Hanauer 2004; Scapa 2015; Wenckert 1978), which were assessed as at unclear risk of bias. Two studies failed to describe whether the placebo was sufficiently identical to the intervention to blind study participants (Florent 1996; Hanauer 2004), and three studies provided insufficient information to permit an objective assessment (Caprilli 2003; Scapa 2015; Wenckert 1978). D'Haens 2008 was described as a single-blinded study and involved the use of dummy tablets. No other information was provided.

Blinding of outcome assessment

We judged five studies as being at high risk of bias due to non-blinding of outcome assessors (Armuzzi 2013; Bergman 1976; Ewe 1989; Fukushima 2018; Tursi 2014). Fourteen studies that failed to adequately describe blinding were assessed as at unclear risk of detection bias (Ardizzone 2004; Chermesh 2007; Ewe 1999; Fedorak 2015; Florent 1996; Mañosa 2013; Prantera 2002; Regueiro 2016; Reinisch 2010; Savarino 2013; Scapa 2015; Sutherland 1997; Wenckert 1978; Yoshida 2012). We judged the remaining studies as having a low risk of detection bias (Brignola 1995; Caprilli 1994; Caprilli 2003; D'Haens 2008; Gossum 2007; Hanauer 2004; Hellers 1999; Herfarth 2006; Herfarth 2013; Lochs 2000; Lopez Sanroman 2017; Marteau 2006; McLeod 1995; Mowat 2016; Regueiro 2009; Rutgeerts 2005).

Incomplete outcome data

We judged 82% of the included studies as at low risk of attrition bias. We judged five studies as at unclear risk of bias for various reasons. Bergman 1976 reported low and balanced attrition rates across groups, however failed to provide the reasons for attrition. In Sutherland 1997 attrition rates were not specifically reported for the subpopulation of interest. Two studies failed to report how attrition rates (20% and 25% respectively) compared with the event risk, and it was unclear whether this was sufficient to cause bias (Ewe 1999; Regueiro 2016). Scapa 2015 failed to report the number of randomised and withdrawn participants and reasons for withdrawal. The authors were contacted for clarification, however no additional information was provided, except that the study is under preparation for publication. Two studies had incomplete outcome data and were assessed as at high risk of attrition bias (Herfarth 2006; Herfarth 2013). Herfarth 2013 reported an overall attrition rate of 30%, which when compared to the event risk of 24% raised concerns about bias. More than half of the randomised participants in Herfarth 2006 withdrew due to treatment failure and the trial was discontinued. The remaining 28 studies reported attrition rates that were low and balanced across groups, and in one trial (Ewe 1989), although the overall attrition rate was high (37%), when compared to the event risk (60%), it was not sufficient to introduce bias. Hence, these studies were judged as at low risk of bias for this domain.

Selective reporting

Trial registration was available for 11 studies (Fedorak 2015; Fukushima 2018; Herfarth 2013; Lopez Sanroman 2017; Mañosa 2013; Mowat 2016; Regueiro 2009; Regueiro 2016; Reinisch 2010; Scapa 2015; Yoshida 2012). Twenty-seven studies reported all outcomes that were prespecified in the methods section of the published manuscript or in the protocol and were judged as at low risk of reporting bias. We assessed six studies as at high risk of bias for selective reporting for the following reasons: failure to report a prespecified outcome (Chermesh 2007; Florent 1996; Lopez Sanroman 2017); non-reporting of outcomes that were prespecified in the trial registration and refusal to provide data upon request (Scapa 2015); inadequate reporting of secondary outcomes (Fedorak 2015); and failure to report on adverse event outcomes (Ewe 1989). We assessed two studies as at unclear risk of bias for this domain: Herfarth 2006 was published as an abstract with no trial registration or sufficient information in the methods section to permit a judgement, whilst Wenckert 1978 failed to sufficiently report the results for adverse events.

Other potential sources of bias

We judged three studies to be at high risk of bias due to baseline imbalance across groups, Regueiro 2009; Rutgeerts 2005, or for failing to report on baseline characteristics (Bergman 1976). Three studies provided insufficient baseline characteristics of randomised participants to permit a determination of whether there were baseline imbalances and were judged as at unclear risk of bias (Herfarth 2006; Scapa 2015; Wenckert 1978). We assessed 29 studies as at low risk of bias.

All-domain risk of bias

We judged 18 studies at high risk of bias for one or more domains as at 'high' or 'very high' risk of bias (Ardizzone 2004; Armuzzi 2013; Bergman 1976; Caprilli 1994; Chermesh 2007; Ewe 1989; Fedorak 2015; Florent 1996; Fukushima 2018; Herfarth 2006; Herfarth 2013; Lopez Sanroman 2017; Regueiro 2009; Rutgeerts 2005; Savarino 2013; Scapa 2015; Tursi 2014; Yoshida 2012). We assessed risk of bias as low or unclear in 17 studies (Brignola 1995; Caprilli 2003; D'Haens 2008; Ewe 1999; Gossum 2007; Hanauer 2004; Hellers 1999; Lochs 2000; Mañosa 2013; Marteau 2006; McLeod 1995; Mowat 2016; Prantera 2002; Regueiro 2016; Reinisch 2010; Sutherland 1997; Wenckert 1978). We judged four studies as at low risk of bias across all domains (Gossum 2007; Marteau 2006; McLeod 1995; Mowat 2016).

Effects of interventions

See: **Summary of findings for the main comparison** Estimates of effects, credible intervals, and certainty of the evidence for maintenance of surgically induced remission in Crohn's disease; **Summary of findings 2** Estimates of effects, credible intervals, and certainty of the evidence for the maintenance of surgically induced remission in Crohn's disease: BENEFITS; **Summary of findings 3** Estimates of effects, credible intervals, and certainty of the evidence for the maintenance of surgically induced remission in Crohn's disease: BENEFITS; **Summary of findings 4** Interventions for the maintenance of surgically induced remission in Crohn's disease: HARMS

We have reported the risk ratio (RR) for pairwise comparisons and the hazard ratio (HR) for the NMA as planned due to the nature of the data. Our first primary outcome was dichotomous, and the second was survival data. The included studies did not report on time to relapse as survival data, but reported this as a dichotomous outcome instead (i.e. number of relapses). The NMA was carried out in a way that takes time into account using the clog-log link. The pairwise comparison, on the other hand, did not take time into account and was analysed using the RR as intended.

Interventions and comparisons: pairwise comparisons

We performed pairwise comparisons on all the studies that met our inclusion criteria. We first analysed the data included in the NMA (Analyses 1 to 12). This was followed by pairwise comparisons on studies that were not included in the NMA due to concerns about transitivity (Analyses 13 to 17). There were 12 direct comparisons in total, as follows.

- 5-ASA versus placebo (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5)
- 5-ASA versus adalimumab (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4)
- 5-ASA versus purine analogues (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5)
- Antibiotics versus placebo (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4)
- Budesonide versus placebo (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4)
- Infliximab versus adalimumab (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4)
- Inflximab versus purine analogues (Analysis 7.1; Analysis 7.2; Analysis 7.3; Analysis 7.4)
- Probiotics versus placebo (Analysis 8.1; Analysis 8.2; Analysis 8.3)
- Purine analogues versus placebo (Analysis 9.1; Analysis 9.2; Analysis 9.3; Analysis 9.4; Analysis 9.5)
- Purine analogues versus adalimumab (Analysis 10.1; Analysis 10.2; Analysis 10.3; Analysis 10.4)
- Sulfasalazine versus placebo (Analysis 11.1; Analysis 11.2; Analysis 11.3)
- Sulfasalazine + prednisolone versus no treatment (Analysis 12.1)

Interventions and comparisons: network and sensitivity analyses

For the NMA, we focused on three main outcomes: clinical relapse, endoscopic relapse, and withdrawals due to adverse events. Data were insufficient to assess time to relapse, and other outcomes such as histologic relapse, adverse events, and serious adverse events were not sufficiently or objectively reported to permit an NMA. Of the 35 studies that met the inclusion criteria of our review, 26 reported sufficient data on the three outcomes and were included in the network (Table 3). Eleven active treatments (5-ASA, 6-MP, adalimumab, azathioprine, budesonide, metronidazole, ornidazole, infliximab, probiotics, sulfasalazine, sulfasalazine + prednisolone) were studied in the review. However, when azathioprine and 6-MP were lumped together as purine analogues, and metronidazole and ornidazole were lumped as antibiotics, we ended up with nine 'groups' of active treatments. Two studies were three-arm trials (Hanauer 2004; placebo, 5-ASA, and purine analogue; Savarino 2013: 5-ASA, adalimumab, purine analogue). There were a total of 45 comparisons encompassing 2245 randomised participants who experienced a total of 1037 clinical relapses (Table 4). There were 21 comparisons on 1128 randomised participants who experienced a total of 779 endoscopic relapses (Table 5). There were 36 comparisons based on 1498 participants, of which 189 discontinued treatment due to adverse events (Table 6). The number of active treatments studied varied across the three networks: clinical relapse (9 treatments: 21 trials), endoscopic relapse (6 treatments: 12 trials), and withdrawal due to adverse events (8 treatments: 15 trials).

Firstly, we analysed the data using fixed-effect and random-effects models. To compare both models and assess which model had a good fit, we used the DIC estimates. The DIC generated from the clinical relapse (Table 7) and endoscopic relapse (Table 8) data indicated that the fixed-effect model was satisfactory. However, as the difference in DIC was less than the stipulated threshold of three to five points (see Data synthesis), we decided to use a random-effects model instead to obtain more conservative estimates. For the outcome withdrawal due to adverse events, we found the random-effects model to be a good fit for the data (Table 9). We therefore used the random-effects model for the base-case analysis for all three outcomes. We also compared the fixed-effect and random-effects models in a sensitivity analysis and carried out three additional sensitivity analyses for the primary outcome (clinical relapse) alone. We undertook sensitivity analyses to assess the impact of a failure to conceal allocation, loss to follow-up, and non-blinded outcome assessment by removing studies at high or unclear risk of bias. We also sought to understand the effect of the low-dose 5-ASA assessed in McLeod 1995 and the definitions of clinical relapse in Ewe 1989, Wenckert 1978, and Bergman 1976.

The network plots are presented in Figure 4, Figure 5, and Figure 6. For clinical relapse and withdrawals due to adverse events, around half of the interventions were part of at least one loop and the others were 'hanging'. The endoscopic relapse network was more connected, as most of the interventions were part of at least one loop, and only two were 'hanging' (antibiotics and probiotics).

Figure 4. Network plot - clinical relapse.

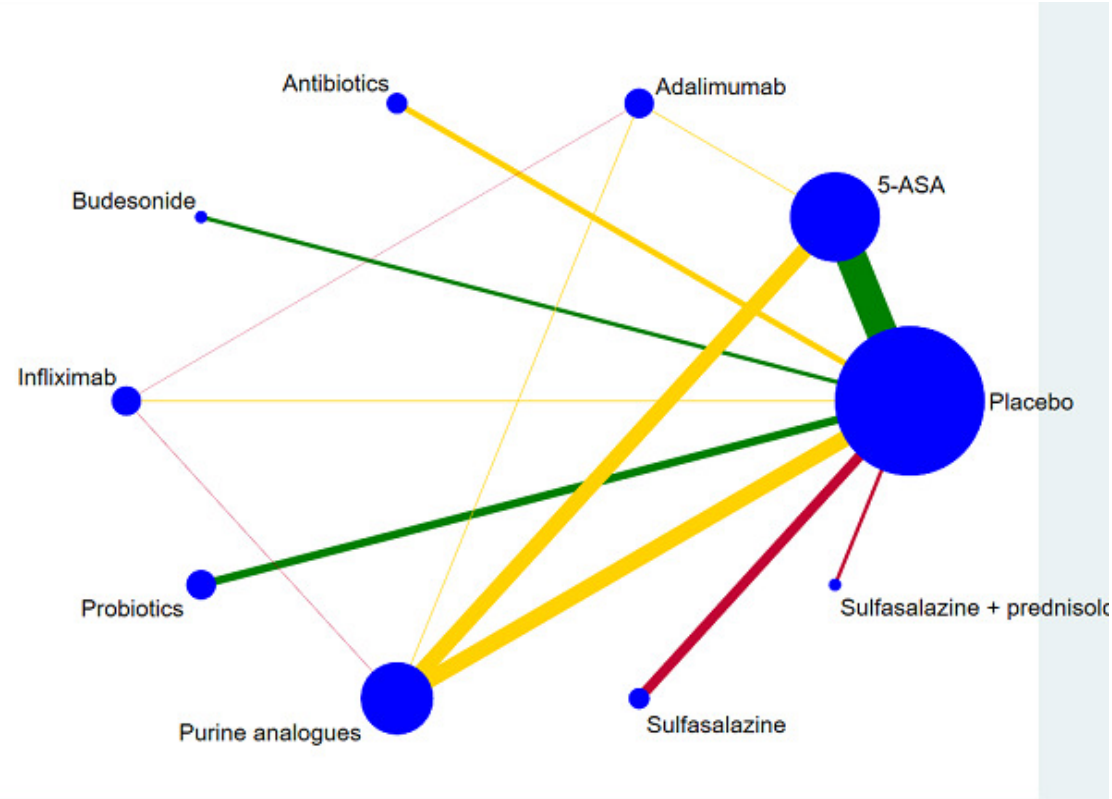


Figure 5. Network plot - endoscopic relapse.

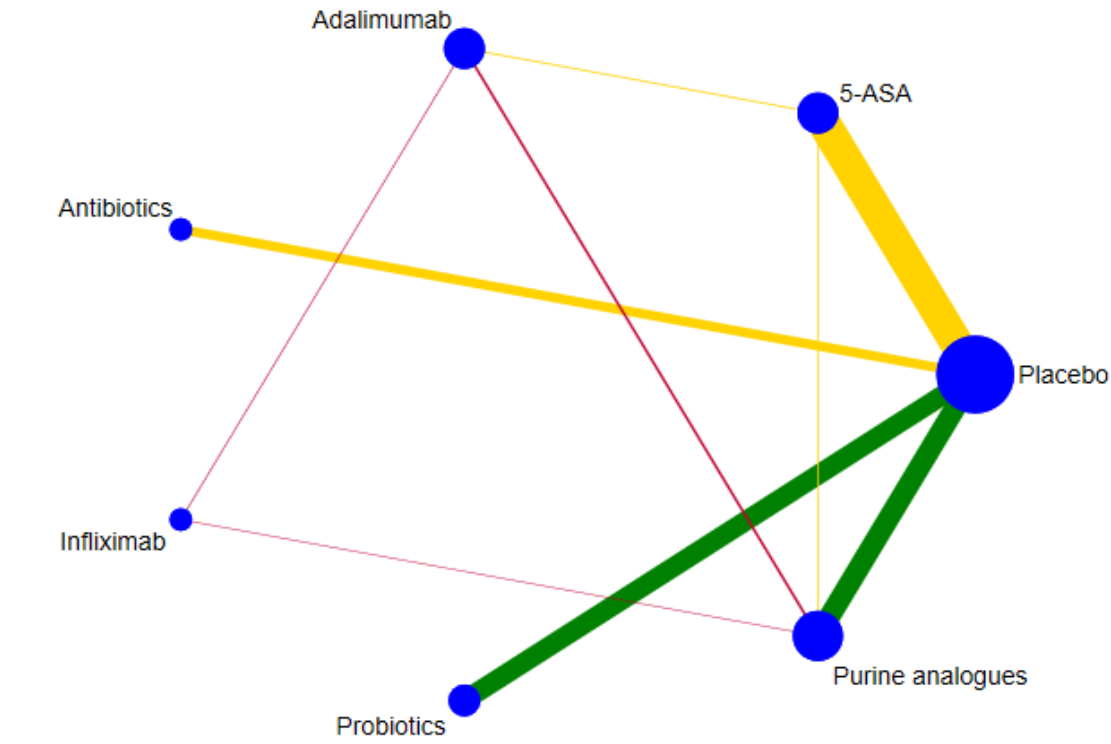
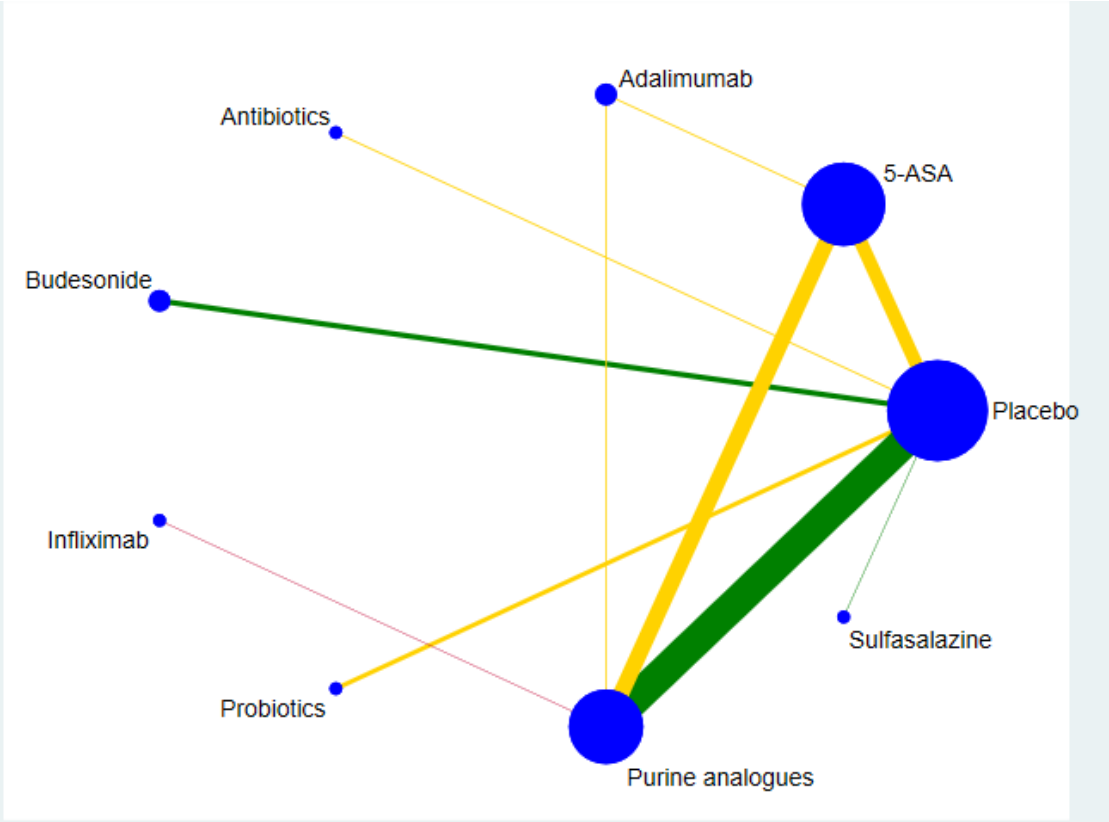


Figure 6. Network plot - withdrawal due to adverse events.



Risk of bias for the base-case network

We assessed risk of bias in three different ways: for the individual studies, where we considered selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias; for each contrast in the network (any pair of interventions in the network) as overall risk of bias by considering the bias for each direct comparison and its percentage contributions to the network estimate; and by calculating the overall risk of bias for the entire network.

Of the 26 studies included in base-case networks for clinical relapse, endoscopic relapse, and withdrawals due to adverse events, three studies were at low risk of bias; nine were at unclear risk of bias; and 14 were at high risk of bias (Figure 2; Figure 3). Studies at low and unclear risk were grouped together, and those at high risk of bias were further divided into high or very high. For the direct comparisons, the overall risk of bias is indicated in the networks and colour coded for the three bias judgments: low/unclear (green), high (yellow), very high (red). Most of the evidence for clinical and endoscopic relapse appeared to be at high or very high risk of bias, whilst evidence for withdrawal due to adverse events was high/very high to low/unclear risk of bias. The overall within-study bias was based on the mean (average) of the three 'Risk of bias' contributions for each contrast (Figure 7; Figure 8; Figure 9).

Figure 7. Clinical relapse: risk of bias contributions of each piece of study to the network estimate; 21 studies: 8 low, 9 moderate, 4 high. Key: green = low/unclear; yellow = high; red = very high overall risk of bias for the contrast.

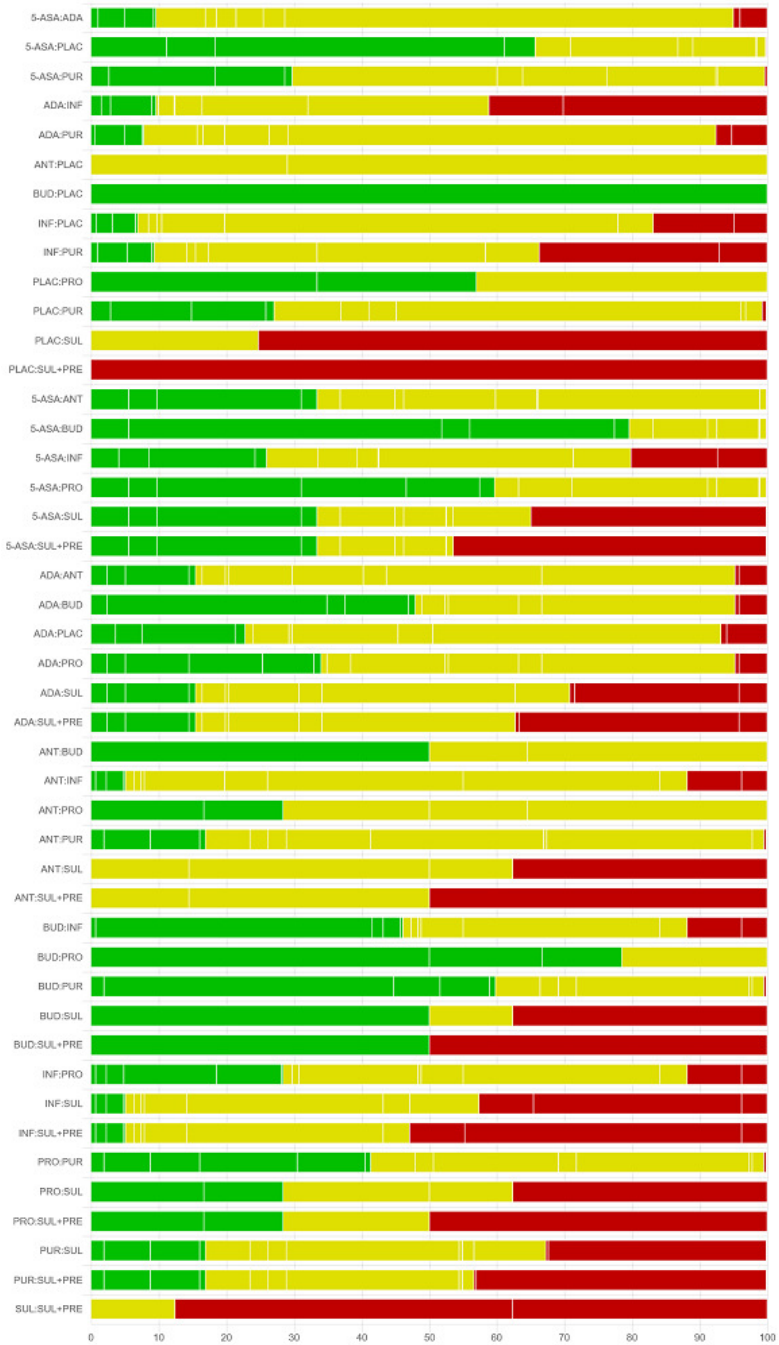


Figure 8. Endoscopic relapse: risk of bias contributions of each piece of study to the network estimate; 12 studies: 4 low, 5 moderate, 3 high. Key: green = low/unclear; yellow = high; red = very high overall risk of bias for the contrast.

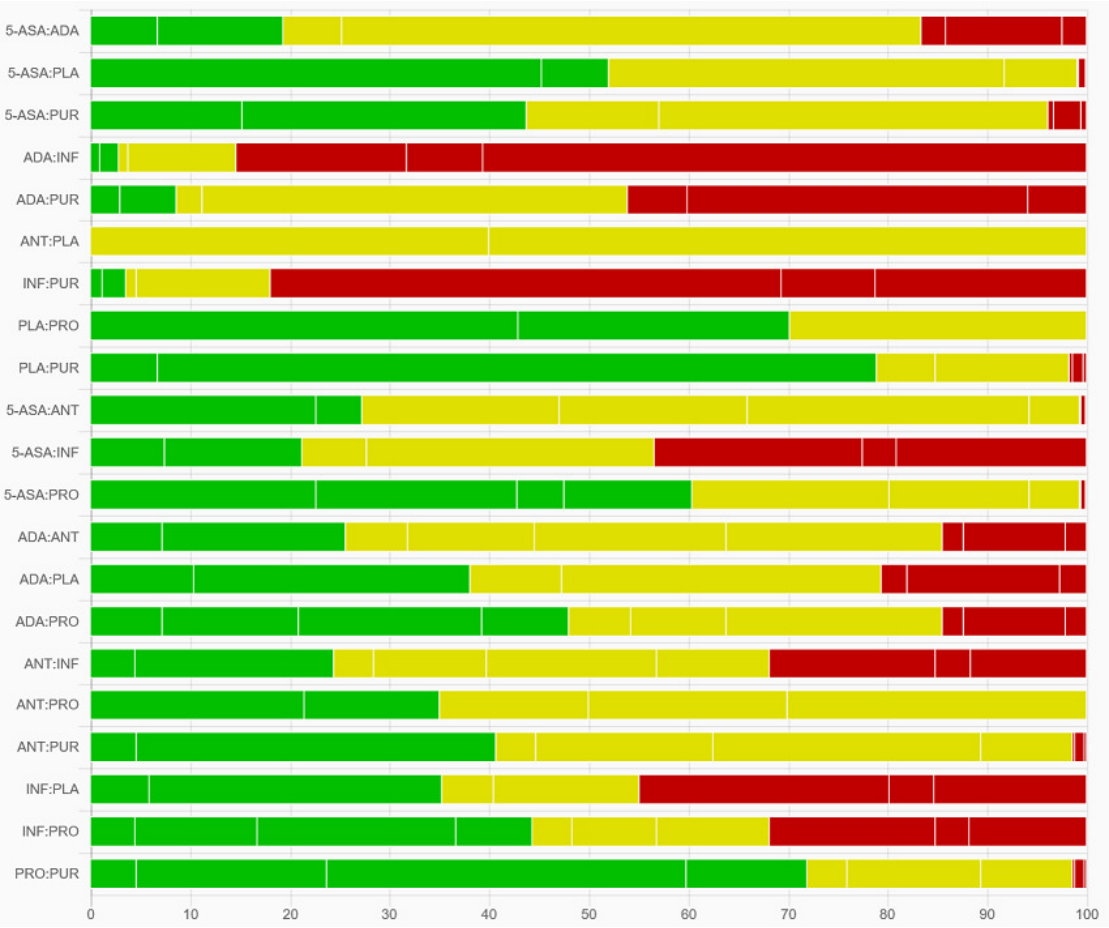
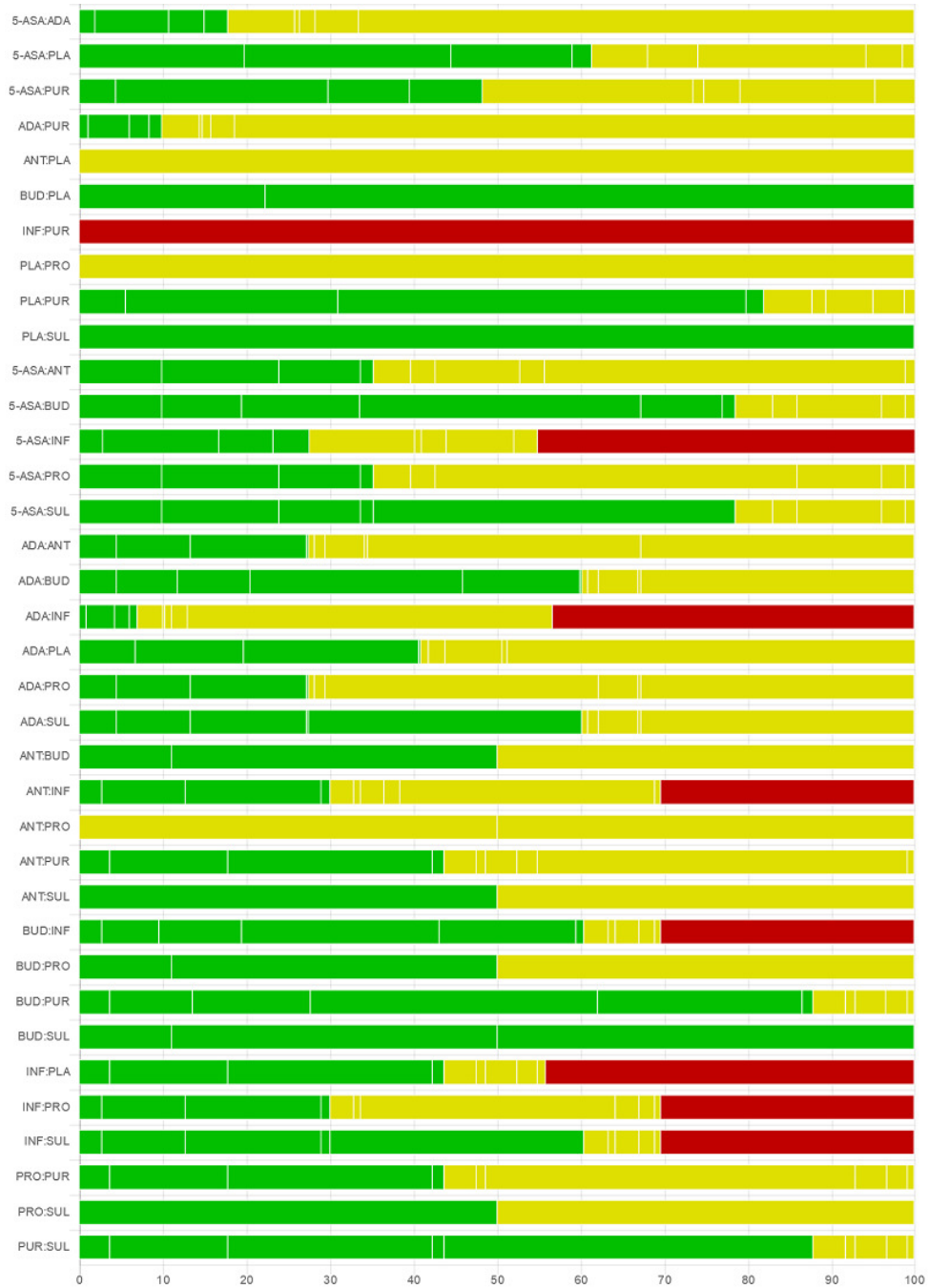


Figure 9. Withdrawal due to adverse events: risk of bias contributions of each piece of study to the network estimate; 15 studies: 7 low, 7 moderate, 1 high. Key: green = low/unclear; yellow = high; red = very high overall risk of bias for the contrast.



Network meta-analysis results

Network meta-analysis results are presented separately for clinical relapse, endoscopic relapse, and withdrawals due to adverse events. We analysed the results as HRs with 95% credible intervals (CrIs) for each contrast (Table 10; Table 11; Table 12); individual treatments (compared to the placebo) (Table 13); and have also displayed these results in forest plots (Figure 10; Figure 11; Figure 12). We then produced a rank order of the interventions in each network (Table 14; Table 15; Table 16), with the probability that a particular intervention is the best, second best, etc. treatment (Figure 13; Figure 14; Figure 15).

Figure 10. Summary plot of clinical relapse showing network estimates of mean hazard ratios (blue diamonds and squares) and their credible intervals (blue horizontal line). Right-hand side = favours named treatment; left-hand side = favours placebo.

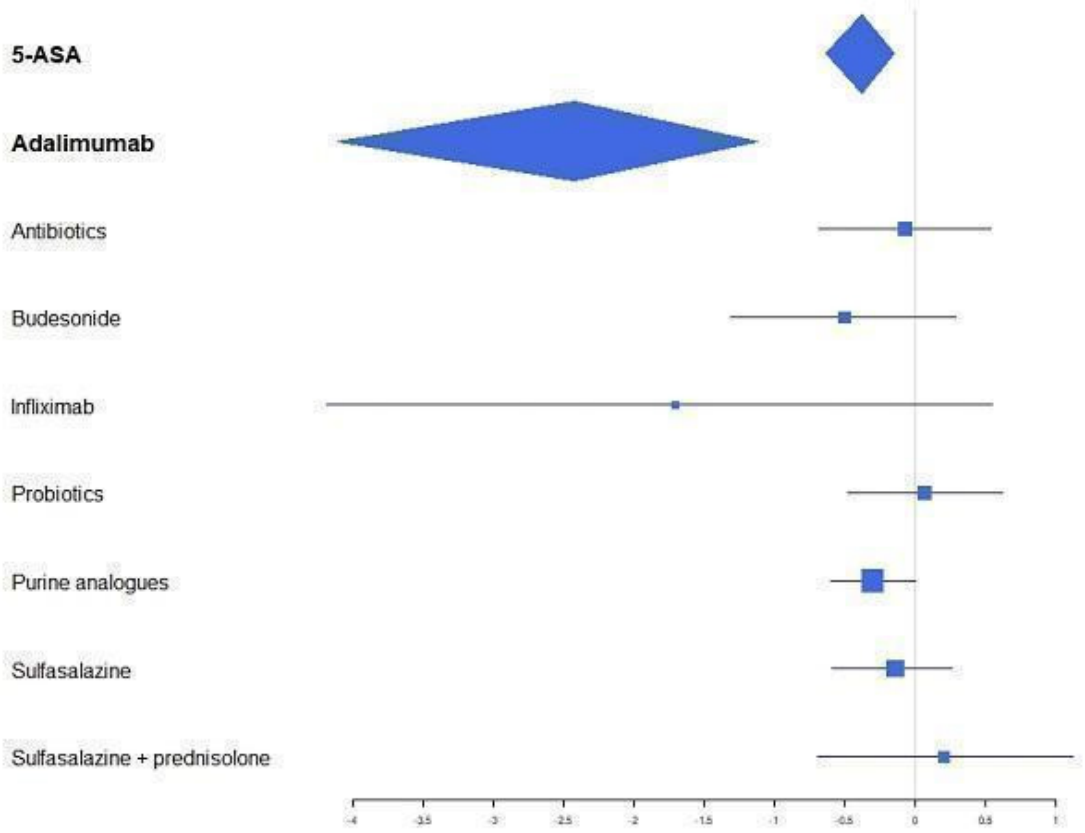


Figure 11. Summary plot of endoscopic relapse showing network estimates of mean hazard ratios (blue diamonds and squares) and their credible intervals (blue horizontal line). Right-hand side = favours named treatment; left-hand side = favours placebo.

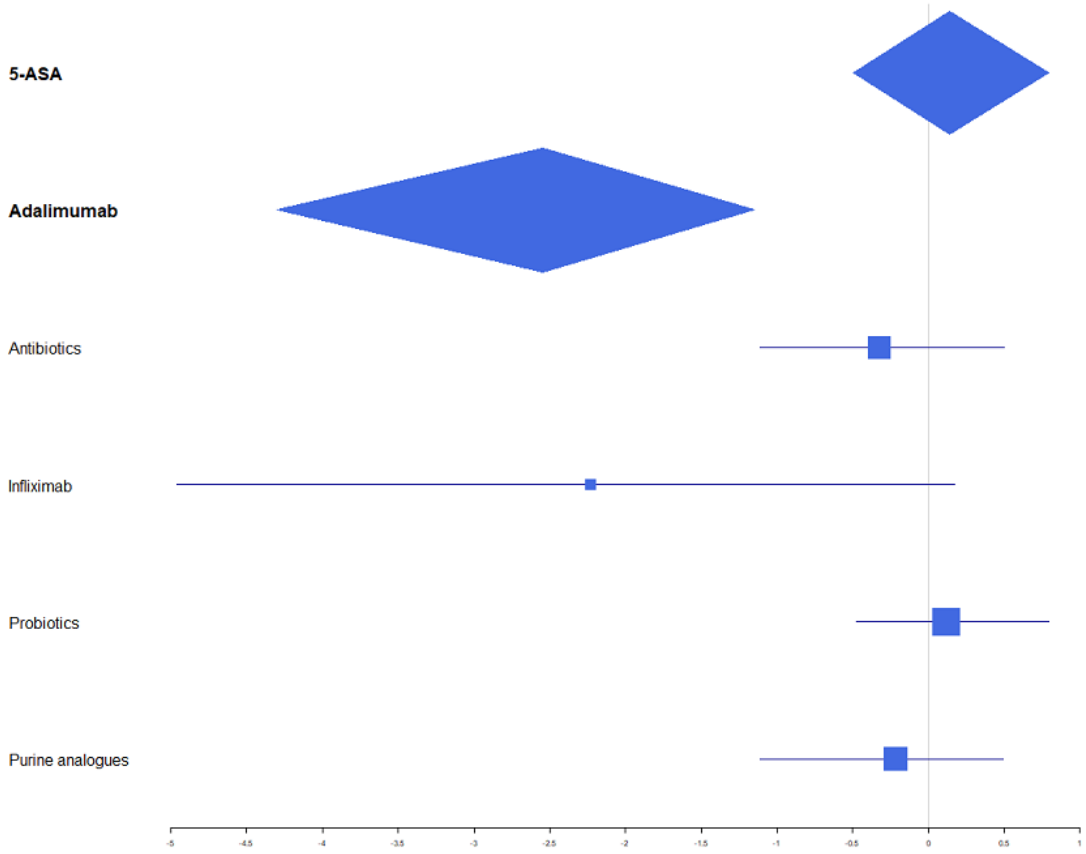


Figure 12. Summary plot of withdrawal due to adverse events showing network estimates of mean hazard ratios (blue diamonds and squares) and their credible intervals (blue horizontal line). Right-hand side favours placebo; left-hand side favours named treatment.

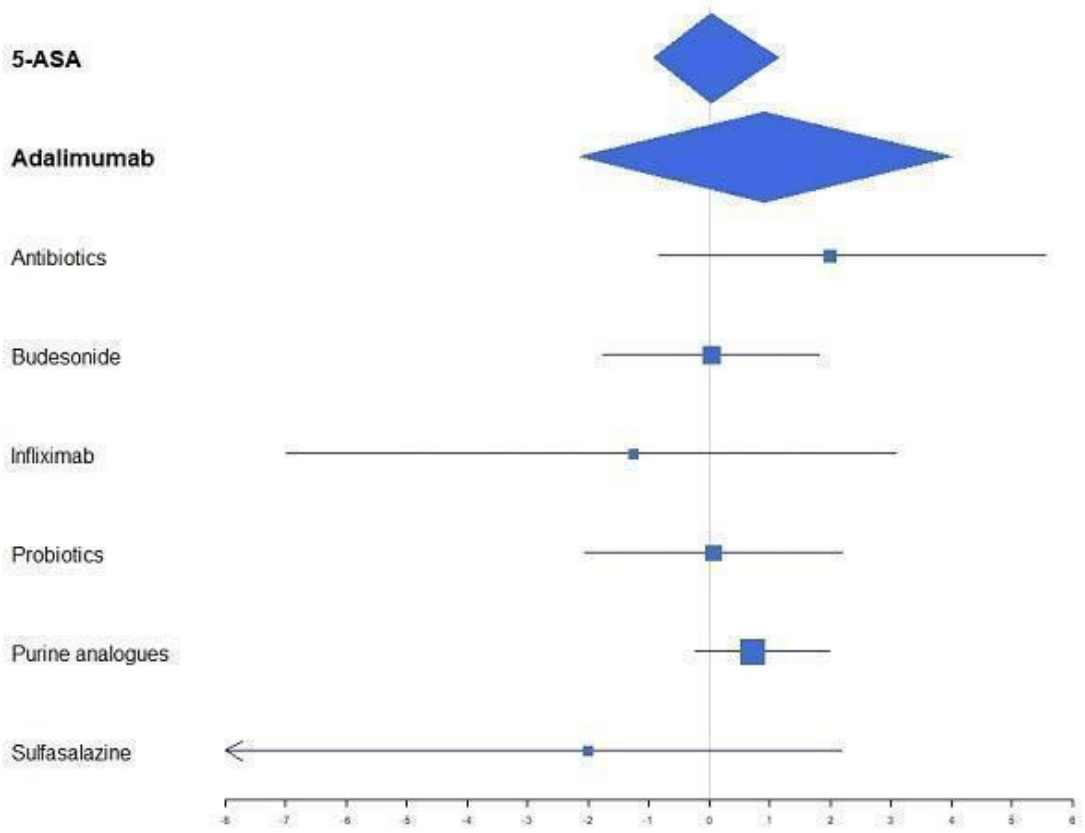


Figure 13. Rank - clinical relapse.

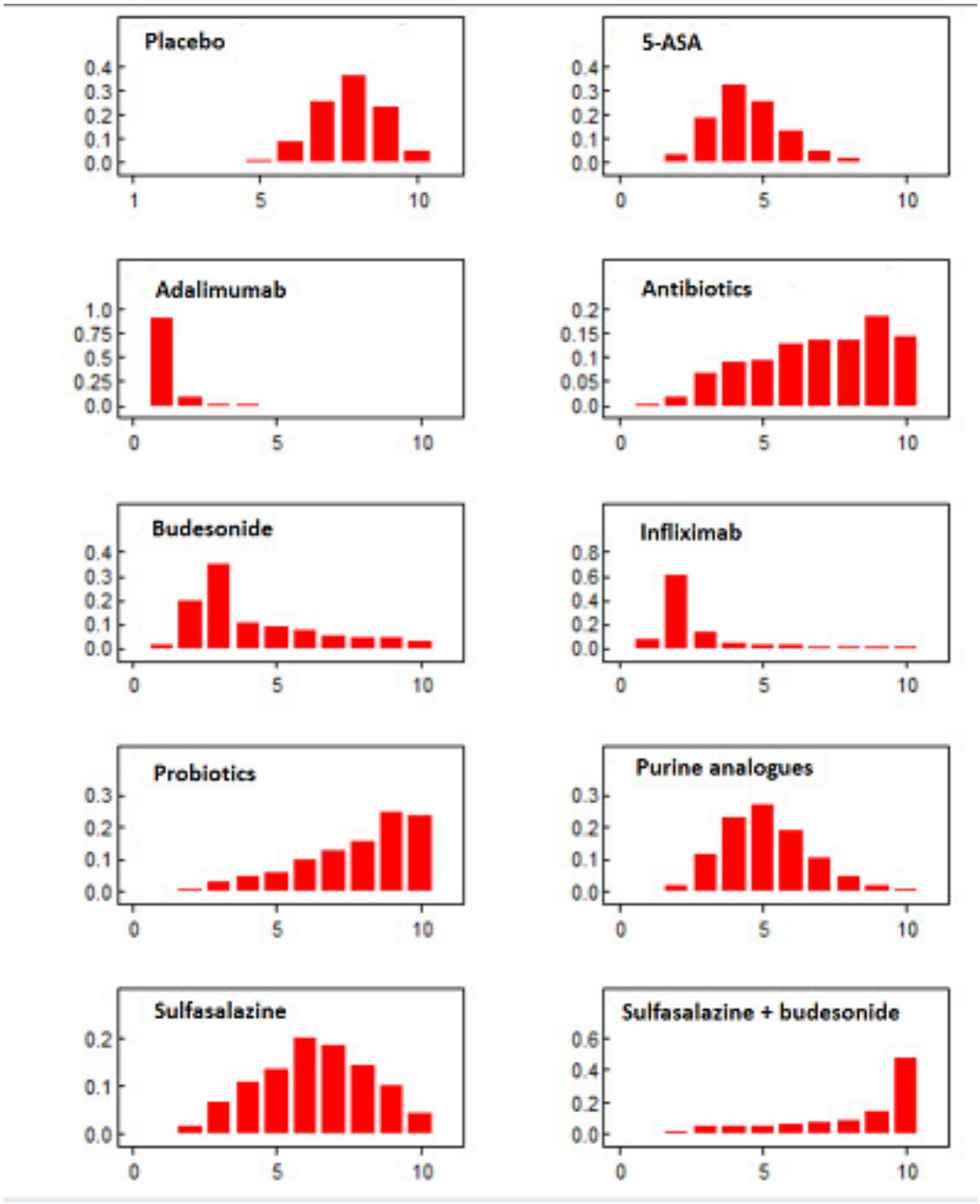


Figure 14. Rank - endoscopic relapse.

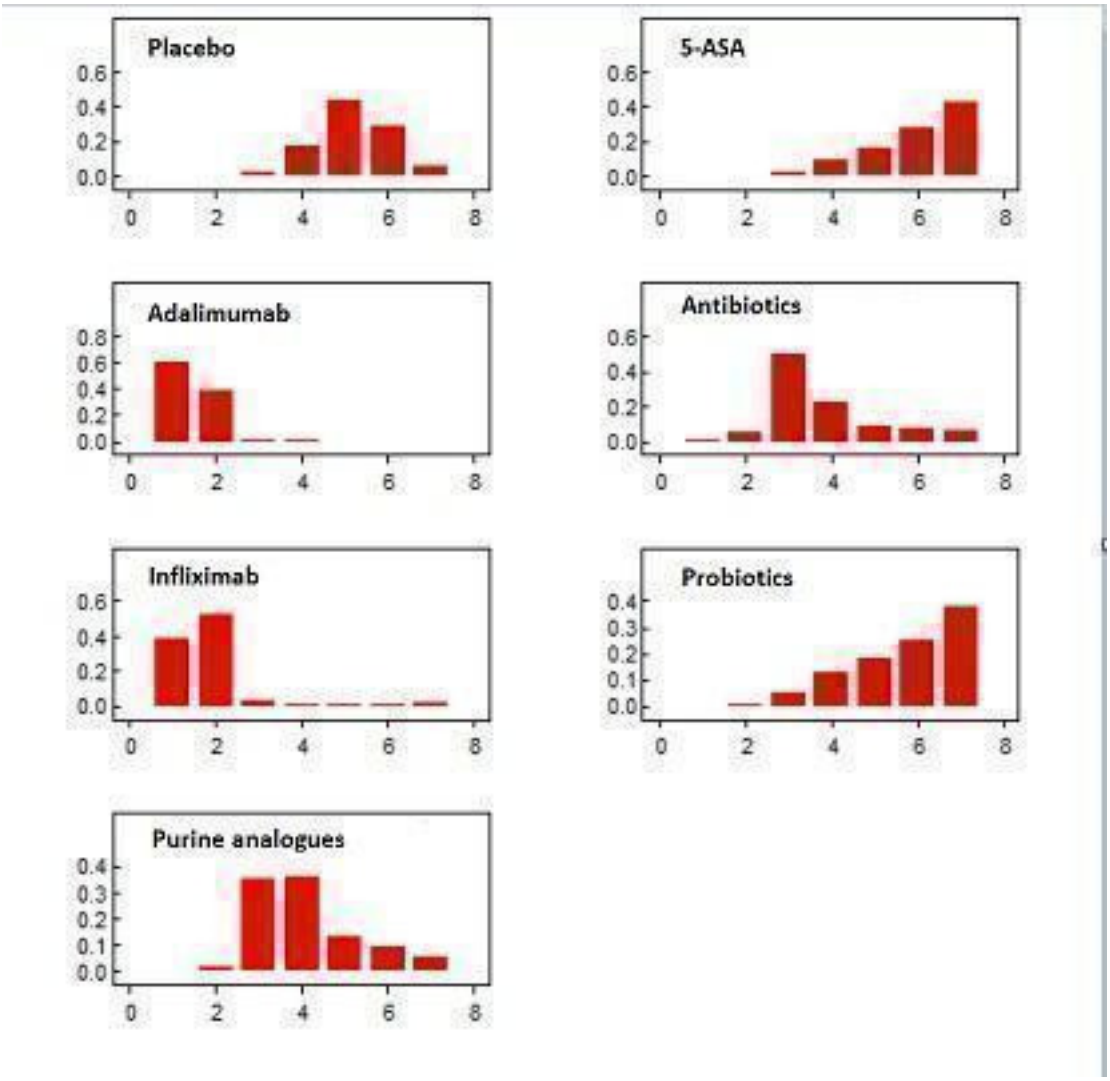
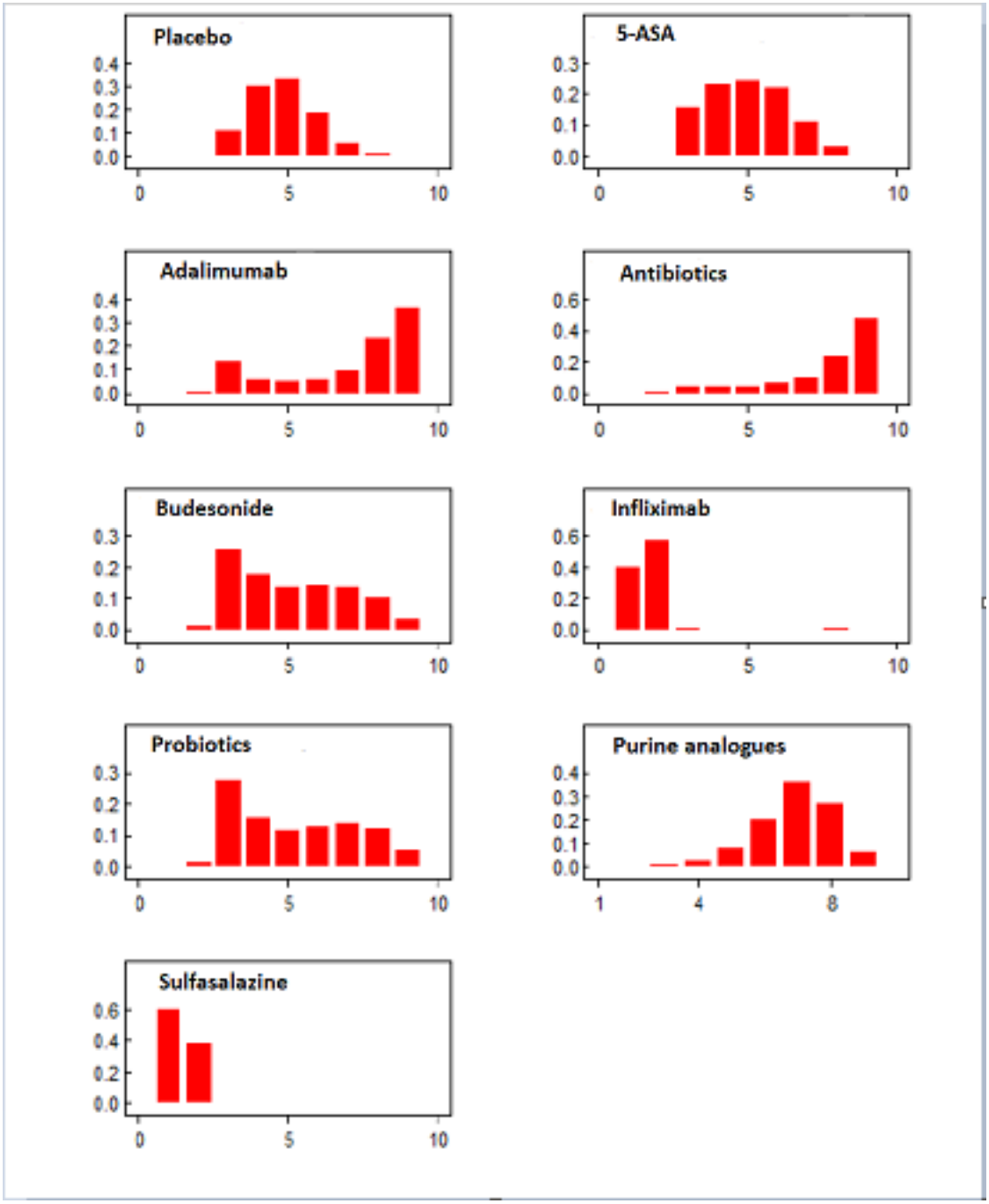


Figure 15. Rank - withdrawal due to adverse events.



Clinical relapse

The analysis generated 45 contrasts, that is all possible pairwise combinations of the interventions. Only 7 out of the 45 contrasts had precise estimates. The rest of the CrIs crossed at least one default minimally important difference, that is the value of 0.75 and 1.25. All 7 contrasts with precise estimates involved adalimumab (versus placebo, 5-ASA, antibiotics, probiotics, purine analogues, sulfasalazine, and sulfasalazine + prednisolone), which was studied in 2 trials with a combined total of 3 events from the 26 participants randomised to receive adalimumab. The results of 85% of the contrasts had imprecision (Table 10; Figure 10).

Endoscopic relapse

There were 21 pairwise combinations of the interventions. Six of the 21 contrasts had precise estimates, whilst the rest of the results included the minimally important difference. Again, all five contrasts with precise estimates involved adalimumab (compared to placebo, 5-ASA, antibiotics, probiotics, and purine analogues). Adalimumab was studied in 3 trials with a combined total of 4 events in the 37 participants randomised to receive it. Results from 71% of the contrasts were imprecise (Table 11; Figure 11).

Withdrawal due to adverse events

For this outcome, the analysis generated 36 contrasts, none of which had precise estimates (Table 12; Figure 12).

Ranking of treatments

We summarised the rank of each intervention as median/range (Table 14; Table 15; Table 16; Table 17) and displayed these in histograms (Figure 13; Figure 14; Figure 15). The closer the mean rank is to 1, the better the efficacy or safety.

Adalimumab was ranked best (mean rank of 1.28) and sulfasalazine + prednisolone worst (mean rank of 8.28) for the outcome clinical relapse (Table 14). The fourth-ranking treatment, 5-ASA, was the only other treatment in the ranking other than adalimumab that was effective. The effect estimates for all comparisons with adalimumab, albeit precise, were based on two small studies. As this ranking does not take into account the certainty of evidence or other outcomes of interest, it should be interpreted with caution (Mbuagbaw 2017). Adalimumab was ranked best (mean rank of 1.4) and 5-ASA worst (mean rank of 5.96) for the outcome endoscopic relapse (Table 15). Sulfasalazine ranked best (mean rank of 2.61) and antibiotics ranked worst (mean rank of 7.82) for the outcome withdrawals due to adverse events (Table 16).

Certainty of the evidence across the whole network

The criteria used for the GRADE assessment of the evidence are reported in Appendix 2. For clinical relapse, the risk of bias across the network was high, and the effect estimates for most of the contrasts (38 out of 45 contrasts) were imprecise. Three out of the seven contrasts with precise credible intervals were influenced by two small studies (Appendix 3), with 26 participants randomised to receive adalimumab, and which show a positive effect in favour of adalimumab. Whilst this raises concerns over publication bias, these contrasts were not found to contribute substantially to the network (Appendix 4). There was no indirectness, however there was marginal inconsistency within the contrasts, although it had no observable impact on the overall network (DIC inconsistency > DIC consistency: 246.27 versus 244.26). The evidence was downgraded twice (once for risk of bias and once for imprecision), and the network classed as being of low certainty (Appendix 5).

Most of the studies that reported on endoscopic relapse were at high risk of bias (66.7%), and most of the contrasts (71%) had imprecise results. Precision in the network, which was noted in 5 contrasts, could be attributed to the 3 small studies that reported 4 events in 37 participants who received adalimumab (Appendix 6). The contrasts involving these small studies showed a positive effect in favour of adalimumab, therefore publication bias is suspected. There was no indirectness. However, we found marginal inconsistency within the contrasts, which had no impact on the network (DIC inconsistency > DIC consistency: 135.70 versus 133.43). The evidence was downgraded twice (once for risk of bias and once for imprecision), and the network classed as being of low certainty (Appendix 7; Appendix 8).

Of the 15 trials that reported data on withdrawals due to adverse events, nine (60%) were at high risk of bias. The results of all contrasts included the minimally important difference of 0.75 or 1.25. Between-study heterogeneity was also noted, however the DIC estimate in the inconsistency model was not substantially less than that estimated by the consistency model (149.36 versus 151.73), therefore we decided not to downgrade the network for inconsistency. We downgraded the evidence twice (once for risk of bias and once for imprecision), resulting in low-certainty evidence (Appendix 9; Appendix 10; Appendix 11).

When we investigated the three networks for publication bias, there was no evidence of asymmetry in the funnel plots (Figure 16; Figure 17; Figure 18), therefore we did not downgrade for publication bias.

Figure 16. Funnel plot for the clinical relapse network showing comparison-specific pooled effect sizes; 1 = placebo; 2 = 5-ASA; 3 = adalimumab; 4 = antibiotics; 5 = budesonide; 6 = infliximab; 7 = probiotics; 8 = purine analogues; 9 = sulfasalazine; 10 = sulfasalazine + prednisolone.

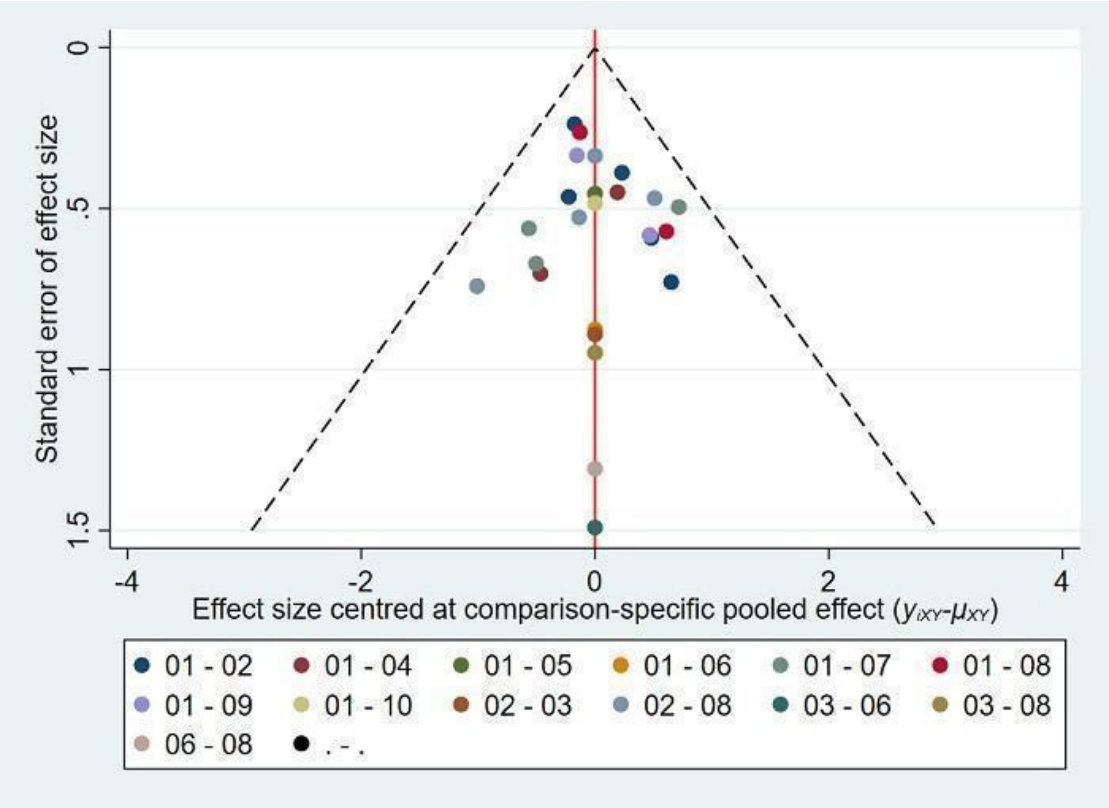


Figure 17. Funnel plot for the endoscopic relapse network showing comparison-specific pooled effect sizes; 1 = placebo; 2 = 5-ASA; 3 = adalimumab; 4 = antibiotics; 5 = infliximab; 6 = probiotics; 7 = purine analogues.

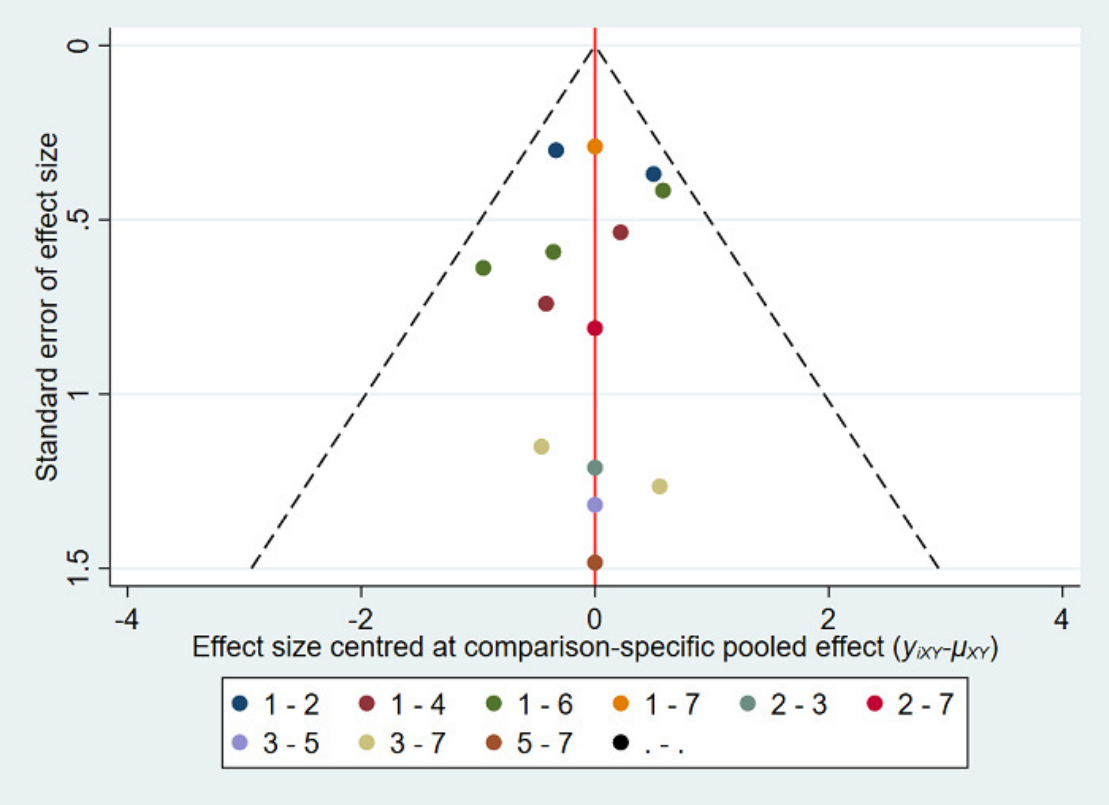
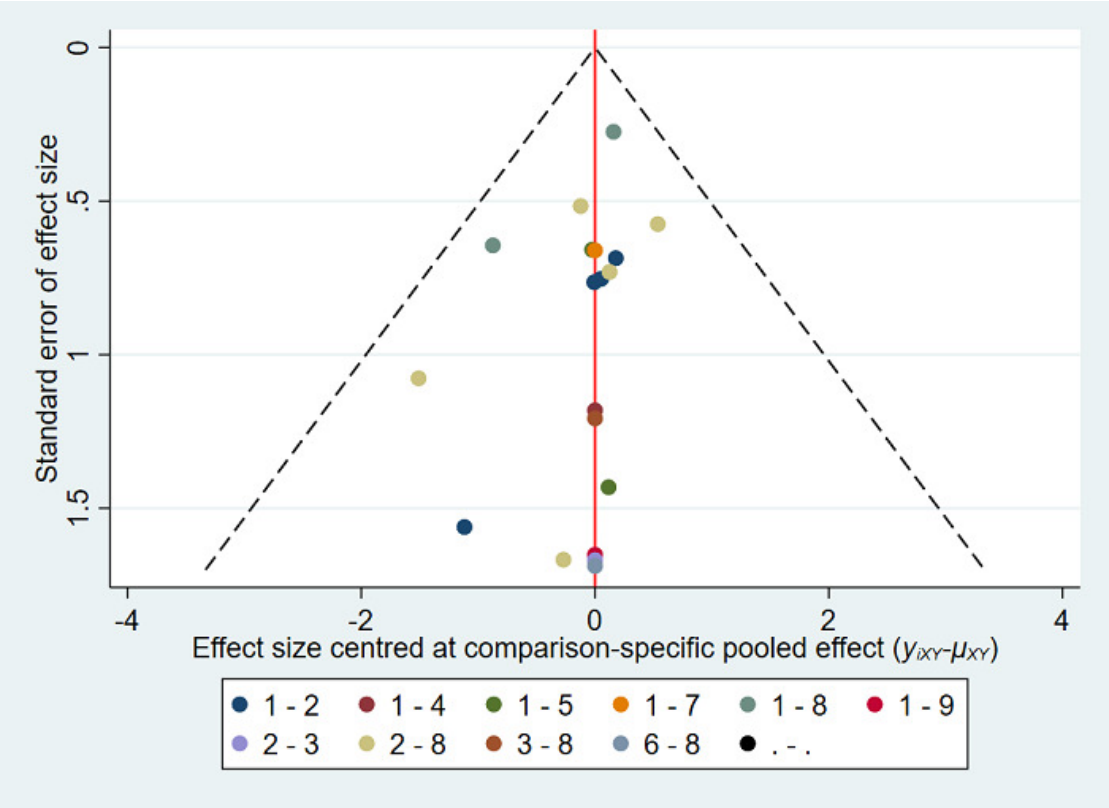


Figure 18. Funnel plot for the withdrawal due to adverse events network showing comparison-specific pooled effect sizes; 1 = placebo; 2 = 5-ASA; 3 = adalimumab; 4 = antibiotics; 5 = budesonide; 6 = infliximab; 7 = probiotics; 8 = purine analogues; 9 = sulfasalazine.



Results and quality assessment for comparisons between individual treatments and reference

For the primary outcome we presented results of the top five interventions. Then we assessed how well these interventions performed with endoscopic relapse and withdrawal due to adverse events. The plan was to use the top-ranking interventions of the primary outcome as a basis for which treatments to focus on in subsequent outcomes (Summary of findings for the main comparison).

Clinical relapse

We compared individual treatments with placebo to further examine the results of the NMA. Given that there had been no previous decision as to which treatments are further assessed, we considered the top five (50%) interventions studied. These were adalimumab, infliximab, budesonide, 5-ASA, and purine analogues. The results from these comparisons are shown in Summary of findings 2. We used CINeMA methods for assessing the certainty of evidence (CINeMA 2017). The HRs varied across the treatment comparisons, with certainty of evidence ranging from very low to moderate. There was low-certainty evidence that adalimumab may prevent clinical relapses (HR 0.11, 95% credible interval (CrI) 0.02 to 0.33; downgraded twice for across-study bias and imprecision). The evidence on infliximab was uncertain, as the certainty was rated as very low (HR 0.36, 95% CrI 0.02 to 1.74; downgraded twice for within-study bias and once for imprecision). There was low-certainty evidence that budesonide may lead to no clear difference in clinical relapse (HR 0.66, 95% CrI 0.27 to 1.34; downgraded twice for imprecision). There was moderate-certainty evidence that 5-ASA may prevent clinical relapse compared with placebo (HR 0.69, 95% CrI 0.53 to 0.87; downgraded for some within-study bias and incoherence). The certainty of the evidence for the effect of purine analogues on clinical relapse compared to placebo was low (HR 0.75, 95% CrI 0.55 to 1.00; downgraded for risk of bias and imprecision) (Figure 10; Table 10; Table 13).

Endoscopic relapse

The certainty of the evidence was either low or very low for this outcome (Summary of findings 3). There was low-certainty evidence that adalimumab may prevent endoscopic relapses (HR 0.10, 95% CrI 0.01 to 0.32; downgraded twice for within-study bias and some incoherence). There was low-certainty evidence that infliximab may lead to no clear difference in endoscopic relapse rates compared to placebo (HR 0.24, 95% CrI 0.01 to 1.20; downgraded twice for within-study bias and imprecision). The evidence for the effect of purine analogues on endoscopic relapse was uncertain because the certainty was rated as very low (HR 0.85, 95% CrI 0.33 to 1.61; downgraded twice for within-study bias and twice for imprecision). The evidence for the effect of 5-ASA on endoscopic relapse was uncertain because the certainty was rated as very low (HR 1.22, 95% CrI 0.61 to 2.18; downgraded twice for within-study bias and twice for imprecision) (Figure 11; Table 11; Table 13).

Withdrawal due to adverse events

When we evaluated withdrawal due to adverse events, the treatments were ordered as follows: infliximab, 5-ASA, budesonide, purine analogues, and adalimumab. We excluded treatments that were not ranked among the top-five treatments for clinical relapse from this list (see above). The aim of this was to gain insight into how well the top treatments for clinical relapse perform with other outcomes. The effect of infliximab, 5-ASA, budesonide, purine analogues, and adalimumab on withdrawal due to adverse events was uncertain (Summary of findings 4). The evidence was downgraded twice for within-study bias and imprecision (Figure 12; Table 12; Table 13).

When considering the network as a whole, two adverse events leading to study withdrawal (i.e. pancreatitis and leukopenia) occurred in more than 1% of participants treated with an intervention. Pancreatitis occurred in 2.8% (11/399) of purine analogue participants compared to 0.17% (2/1210) of all other groups studied. Leukopenia occurred in 2.5% (10/399) of purine analogue participants compared to 0.08% (1/1210) of all other groups studied.

Comparison of results from the network meta-analysis with the direct evidence

Of the four contrasts with more than one study reporting on clinical relapse, three contrasts had an I^2 of 0%, and one contrast (probiotics versus placebo) had an I^2 of 49% (Analysis 8.1). However, the evidence was not downgraded as the I^2 was considered to be low. For endoscopic relapse, two (5/12 studies: 5-ASA versus placebo and probiotics versus placebo) out of five contrasts had an I^2 of 53% and were downgraded once for moderate inconsistency (Analysis 1.5; Analysis 8.3). One of the three contrasts with multiple studies (2/14 studies: purine analogues versus placebo) that reported on withdrawal due to adverse events had an I^2 of 51% and was downgraded for moderate inconsistency (Analysis 9.4). The inconsistency model fitted for clinical and endoscopic relapse networks did not show any incoherence between the direct and indirect evidence (Table 18; Table 19). When we assessed the safety data for inconsistency, we noted lower DIC estimates for the inconsistency model (140.01) compared to the consistency model (142.41) (Table 20). The difference (i.e. < 3) between these models was considered insufficient to warrant downgrading of the evidence. For the contrasts, we noted and downgraded the evidence for the following contrasts:

- clinical relapse: adalimumab versus purine analogues; purine analogues versus placebo;
- endoscopic relapse: 5-ASA versus adalimumab; adalimumab versus purine analogues; and
- withdrawal due to adverse event: 5-ASA versus purine analogues contrast in the network.

Sensitivity analysis

We carried out sensitivity analyses to assess the impact of our choice of model, bias, variation in dose of 5-ASA, direction of treatment effect, and definition of clinical relapse on the primary outcome (Table 21). We excluded two studies assessing antibiotics and probiotics that were not consistent with the other trials. This resulted in similar results to the main analysis, except for antibiotics and probiotics, which showed a slightly increased effect size. Due to high risk of bias in the studies, we only had a limited amount of data to assess for the sensitivity analyses, therefore not all interventions were analysed. The results of the sensitivity analyses remained consistent with the main analyses for all the interventions studied except purine analogues. Compared to the main analysis (random-effects model: HR 0.75, 95% CrI 0.55 to 1.00), purine analogues appeared to be slightly beneficial in preventing clinical relapse with the fixed-effect model (HR 0.75, 95% CrI 0.58 to 0.94). This was also observed when we analysed studies at low risk of selection bias due to allocation concealment (random-effects: HR 0.68, 95% CrI 0.43 to 0.98). When we removed studies at high risk of detection bias, the results were similar to those obtained from the main analysis for all interventions assessed . Given the limited amount of data and inconsistency, these results should be interpreted with caution.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

BENEFITS

Estimates of effects, credible intervals, and certainty of the evidence for the maintenance of surgically induced remission in Crohn's disease

Patient or population: surgically induced remission in Crohn's disease
Settings: hospital, home, or combination
Intervention: 5-ASA, adalimumab, antibiotics, budesonide, infliximab, probiotics, purine analogues, sulfasalazine, sulfasalazine + prednisolone
Comparator (reference): placebo
Outcome: clinical relapse; range of follow-up between 3 and 36 months

Total studies: 20 RCTs Total participants: 2149	**Relative effect (95% CrI)***	**Certainty of the evidence (GRADE)**	**Ranking (95% CrI)****
Adalimumab (2 RCTs; 26 participants)	**HR** 0.11 (0.02 to 0.33) Network estimate	⊕⊕◯◯ **low**[1,2]	1 (1 to 2)
Infliximab (2 RCTs; 21 participants)	**HR** 0.36 (0.02 to 1.74) Network estimate	⊕◯◯◯ **very low**[2,3]	2 (1 to 10)
Budesonide (1 RCT; 43 participants)	**HR** 0.66 (0.27 to 1.34) Network estimate	⊕⊕◯◯ **low**[2,4]	3 (2 to 10)
5-ASA (9 RCTs; 542 participants)	**HR** 0.69 (0.53 to 0.87) Network estimate	⊕⊕⊕◯ **moderate**[2,5]	4 (2 to 7)
Purine analogues (6 RCTs; 316 participants)	**HR** 0.75 (0.55 to 1.00) Network estimate	⊕⊕◯◯ **low**[2,6]	5 (3 to 8)
Sulfasalazine (2 RCTs; 143 participants)	**HR** 0.89 (0.55 to 1.30) Network estimate	⊕◯◯◯ **very low**[2,3]	6 (3 to 10)
Antibiotics (2 RCTs; 57 participants)	**HR** 0.98 (0.50 to 1.71) Network estimate	⊕◯◯◯ **very low**[2,3]	7 (3 to 10)

Probiotics (2 RCTs; 105 participants)	**HR** 1.11 (0.62 to 1.88) Network estimate	⊕◯◯◯ **very low**[2,3]	8 (3 to 10)
Sulfasalazine + prednisolone (1 RCT; 57 participants)	**HR** 1.37 (0.50 to 3.07) Network estimate	⊕◯◯◯ **very low**[2,3]	9 (3 to 10)
Placebo (16 RCTs; 935 participants)	Reference comparator	Not estimable	8 (6 to 10)

*Estimates are reported as hazard ratio (HR), credible interval (CrI). Results are expressed in credible intervals as opposed to confidence intervals as a Bayesian analysis has been conducted

**Median rank and credible intervals for efficacy outcome are presented. Rank statistics are defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on, effective treatment

5-ASA: 5-aminosalicylic acid; RCT: randomised controlled trial

GRADE Working Group grades of evidence

High certainty: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: We are very uncertain about the estimate.

[1]Downgraded two levels: once due to high risk of bias and once for imprecision.

[2]There was no significant intransitivity, with comparable distribution of plausible effect modifiers across trials of different interventions for maintenance of remission.

[3]Downgraded three levels: once due to high risk of bias and twice for imprecision.

[4]Downgraded two levels for imprecision.

[5]Downgraded one level for high risk of bias.

[6]Downgraded two levels: once for risk of bias and once for inconsistency in the evidence.

BENEFITS

Estimates of effects, credible intervals, and certainty of the evidence for the maintenance of surgically induced remission in Crohn's disease

Patient or population: surgically induced remission in Crohn's disease
Settings: hospital, home, or combination
Intervention: 5-ASA, adalimumab, antibiotics, infliximab, probiotics, purine analogues
Comparator (reference): placebo
Outcome: endoscopic relapse; range of follow-up between 3 and 36 months

Total studies: 12 RCTs Total participants: 1128	**Relative effect (95% CrI)***	**Certainty of the evidence (GRADE)**	**Ranking (95% CrI)****
Adalimumab (3 RCTs; 37 participants)	**HR** 0.10 (0.01 to 0.32) Network estimate	⊕◯◯◯ **low**[1,2]	1 (1 to 2)
Infliximab (2 RCTs; 21 participants)	**HR** 0.24 (0.01 to 1.20) Network estimate	⊕⊕◯◯ **low**[1,2]	2 (1 to 6)
Antibiotics (2 RCTs; 57 participants)	**HR** 0.80 (0.33 to 1.65) Network estimate	⊕◯◯◯ **very low**[2,3]	3 (2 to 7)
Purine analogues (4 RCTs; 164 participants)	**HR 0.85** (0.33 to 1.61) Network estimate	⊕◯◯◯ **very low**[2,3]	4 (3 to 7)
Probiotics (3 RCTs; 108 participants)	**HR 1.20** (0.62 to 2.19) Network estimate	⊕◯◯◯ **very low**[2,3]	6 (3 to 7)
5-ASA (3 RCTs; 237 participants)	**HR** 1.22 (0.61 to 2.18) Network estimate	⊕◯◯◯ **very low**[2,3]	6 (3 to 7)
Placebo (8 RCTs; 507 participants)	Reference comparator	No estimate	5 (3 to 7)

*Estimates are reported as hazard ratio (HR), credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals as a Bayesian analysis has been conducted

**Median rank and credible intervals for efficacy outcome are presented. Rank statistics are defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on, effective treatment

5-ASA: 5-aminosalicylic acid; RCT: randomised controlled trial

GRADE Working Group grades of evidence

High certainty: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: We are very uncertain about the estimate.

[1]Downgraded two levels: once due to high risk of bias and once for imprecision.

[2]There was no significant intransitivity, with comparable distribution of plausible effect modifiers across trials of different interventions for maintenance of remission.

[3]Downgraded three levels: once due to high risk of bias and twice for imprecision.

HARMS

Interventions for the maintenance of surgically induced remission in Crohn's disease

Patient or population: surgically induced remission in Crohn's disease
Settings: hospital, home, or combination
Intervention: 5-ASA, adalimumab, antibiotics, budesonide, infliximab, probiotic, purine analogues, sulfasalazine
Comparison: placebo
Outcome: withdrawal due to adverse events; range of follow-up between 3 and 36 months

Total studies: 14 RCTs Total participants: 1419	**Relative effect (95% CrI)***	**Certainty of the evidence (GRADE)**	**Ranking (95% CrI)****
Sulfasalazine (1 RCT; 32 participants)	**HR** 1.96 (3.04E-04 to 8.90)	⊕◯◯◯ **very low**[1,2]	2 (1 to 9)
Infliximab (1 RCT; 11 participants)	**HR** 6.37 (9.14E-04 to 21.74)	⊕◯◯◯ **very low**[1,2]	2 (1 to 9)
5-ASA (8 RCTs; 371 participants)	**HR** 1.19 (0.39 to 3.14)	⊕◯◯◯ **very low**[1,2]	4 (2 to 7)
Budesonide (2 RCTs; 106 participants)	**HR** 1.64 (0.17 to 6.19)	⊕◯◯◯ **very low**[1,2]	4 (1 to 9)
Probiotic (1 RCT; 58 participants)	**HR** 2.44 (0.13 to 9.00)	⊕◯◯◯ **very low**[1,2]	5 (1 to 9)
Adalimumab (1 RCT; 16 participants)	**HR** 11.74 (0.12 to 55.06)	⊕◯◯◯ **very low**[1,2]	7 (1 to 9)
Purine analogues (7 RCTs; 315 participants)	**HR** 2.51 (0.79 to 7.35)	⊕◯◯◯ **very low**[1,2]	7 (4 to 9)
Antibiotics (1 RCT; 16 participants)	**HR** 53.92 (0.43 to 259.80)	⊕◯◯◯ **very low**[1,2]	9 (2 to 9)

Placebo (10 RCTs; 531 participants)	Reference comparator	No estimate	4 (2 to 7)

*Estimates are reported as hazard ratio (HR), credible interval (CrI). Results are expressed in credible intervals as opposed to confidence intervals as a Bayesian analysis has been conducted

**Median rank and credible intervals for efficacy outcome are presented. Rank statistics are defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on, effective treatment

5-ASA: 5-aminosalicylic acid; RCT: randomised controlled trial

GRADE Working Group grades of evidence

High certainty: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: We are very uncertain about the estimate.

[1]Downgraded three levels: once due to high risk of bias and twice for imprecision across the network.

[2]There was no significant intransitivity, with comparable distribution of plausible effect modifiers across trials of different interventions for maintenance of remission.

DISCUSSION

Summary of main results

The NMA conducted to determine the effectiveness of interventions for maintaining surgically induced remission in Crohn's disease assessed three main outcomes: clinical relapse, endoscopic relapse, and withdrawal due to adverse events (Summary of findings for the main comparison). The results from the network for prevention of clinical relapse (21 studies) demonstrate just two therapies as effective (Summary of findings 2): adalimumab (ranked first) and 5-ASA (mesalazine, ranked fourth). These results were consistent with the direct evidence (Gjuladin-Hellon 2019a; Gjuladin-Hellon 2019b). Analysis of a study comparing adalimumab, purine analogues, and 5-ASA demonstrated that adalimumab was more effective for preventing clinical relapse, with one study comparing adalimumab with infliximab finding no difference in relapse rates. The direct evidence for 5-ASA also shows effectiveness for preventing clinical relapse when compared to placebo, and no difference in relapse rates when compared to purine analogues (Gjuladin-Hellon 2019a). There was little or no difference in prevention of clinical relapse with budesonide when compared with placebo. Purine analogues were shown to lead to a slight reduction in clinical relapse rates when a fixed-effect model was used, however this effect was not sustained with a random-effects model (the main analysis). Due to concerns about inconsistency and risk of bias, we downgraded the evidence to low certainty.

The results for prevention of endoscopic relapse (13 studies) demonstrated just one effective therapy, adalimumab (ranked first) (Summary of findings 3). The direct evidence also demonstrated adalimumab as the only effective therapy for preventing endoscopic relapse across all the possible comparisons from the 13 studies reporting on this outcome.

The results for withdrawal of therapy due to adverse events showed no therapy to be at higher risk for withdrawal in the network (Summary of findings 4). Sulfasalazine was demonstrated to be safe in the network and antibiotics unsafe. In the network, sulfasalazine did not appear to be associated with an increased risk of withdrawal due to adverse events, whilst antibiotics appeared to be associated with an increased risk of withdrawal due to adverse events. However, these results needs to be interpreted with caution given the low certainty of the evidence. The direct evidence for all comparisons showed no difference in rates of withdrawal due to adverse events across studies, except for 5-ASA, which was shown to be superior to purine analogues. Despite the limited evidence across the network, the occurrence of two specific adverse events (i.e. pancreatitis and leukopenia) that led to withdrawal in more than 1% of treated participants must be noted. These adverse events occurred in participants who received purine analogues.

A previous review has demonstrated that adalimumab maintains medically induced remission (Behm 2008), which is consistent with the result found in this NMA. This was not the case for 5-ASA preparations, which are ineffective for maintenance of medically induced remission in Crohn's disease (Akobeng 2016). It is not clear why the evidence suggests a difference in efficacy for 5-ASA agents in patients with medically and surgically induced remission. One possibility is that assessments of disease activity used at study entry may not be comparable. The limitations of a CDAI score within clinical trials has been previously noted (Caprilli 1994), and most of the clinical trials performed to evaluate the role of 5-ASA in the maintenance of medically induced remission defined remission using the CDAI score. As most of the trials involved in this review used surgical resection of macroscopically diseased bowel as their inclusion criterion, it follows that many of these patients may actually have less active disease compared to patients in trials of medically induced remission. This may explain the observed difference in efficacy of 5-ASA agents.

It is also possible that the length of time in remission may partly explain this difference in efficacy. Many of the studies in the review of medically induced remission included patients who had been in remission for significant periods of time at study entry (Akobeng 2016). By contrast, most of the studies in this review required entry and initiation of therapy within 12 weeks of surgery. Evidence obtained from studies with a follow-up of greater than 12 months still favoured the use of 5-ASA agents, but as the longest study follow-up was 36 months, it is possible that if a longer follow-up was used this effect would not be sustained.

The situation with purine analogues is also complex. These drugs have been identified as effective for medically induced maintenance of remission in Crohn's disease (Chande 2015). However, when considering the wider evidence from this medical maintenance review (Chande 2015), meta-analysis when compared with 5-ASA agents did not show superiority. This is consistent with the previous postsurgical remission review (Gjuladin-Hellon 2019b), which did show efficacy versus placebo, but again failed to demonstrate superiority versus 5-ASA. In this NMA, as well as in the previous two, the GRADE rankings for such findings were all low, suggesting that more research is likely to change the findings.

Overall completeness and applicability of evidence

The most important issue to address is the size and breadth of evidence, as this clearly has implications for current practice and future research. The key intervention that has been demonstrated to be effective for preventing both endoscopic and clinical relapse is adalimumab. However, this is based on low-certainty evidence from one study with 26 participants receiving the intervention for prevention of clinical relapse. This clearly limits the applicability of these findings to practice. Indeed, the large HR observed (HR 0.11) is not at a level seen across the field, with just 1 case of clinical relapse seen in adalimumab-treated participants compared with 12 cases in purine analogues and 9 cases in 5-ASA participants. This

raises a real question of imprecision and renders this key result limited in its utility for practice at present.

The evidence for 5-ASA was from a larger evidence base with 9 studies across the network with 542 participants included. This led to a result that was of moderate certainty. Conversely, the evidence for endoscopic relapse was far less complete for 5-ASA, with just three studies (501 participants) reporting on this outcome. Considering the remaining interventions across the network, the evidence is capricious. The evidence for purine analogues was of reasonable size, with 6 studies considering 316 participants who received purine analogues for prevention of clinical relapse. The findings of lack of efficacy across the network for both clinical and endoscopic remission are particularly relevant to practice, as purine analogues are used across the field and feature in a number of international Crohn's disease treatment guidelines (Gionchetti 2017; NICE 2012). For all other agents, the completeness of the evidence (i.e. small number of studies and participants) across the network remains an issue. This imprecision must be considered when interpreting these results for treatments that do not reflect current practice or guidance.

The second major issue that pervaded the network was the heterogeneity of study design, outcome measures employed, and the reporting of these outcomes. Some studies looked at clinical relapse as a key outcome, whilst other studies used endoscopic investigation. The follow-up time varied widely, a key issue that impacts the utility of studies of maintenance of remission. The specific manner in which the two key outcomes were reported varied in minor, but in significant ways that limited the scope for some analyses. In particular, the use of the CDAI involved a number of different thresholds for clinical relapse, and these different thresholds could have had a substantial effect on findings. Similarly, the scoring systems used to report endoscopic relapse were also subject to interstudy variation. A recent process has sought to reach an international consensus on such outcomes and is key for preventing such factors that limit the evidence (Kim 2017).

The assessment of safety was difficult across the studies in this review. Whilst terms such as 'serious adverse event' and 'minor side effects' may seem clear, the reporting of adverse event outcomes was extremely heterogenous across studies. A number of studies only reported occurrence rates or the number of events rather than the actual numbers of participants affected. Similarly, some events were reported as serious adverse events, but were clearly not clinically relevant (e.g. the occurrence of pregnancy). Whilst this may be in line with the individual protocols of the studies, it has made analysis very difficult. This is why we chose to use withdrawal due to adverse events as a key outcome for the NMA, as this outcome is usually reported in a very clear fashion and does have clinical relevance. However, this led to much lower occurrence numbers, and therefore imprecision for this outcome across the network. This limits the completeness of the evidence base for adverse events.

The third issue relates to the use of concomitant therapy. We were unable to include several studies in the network because of concomitant therapies used during part or all of the maintenance period. As these treatments were not randomised, and some were included as active comparators in other parts of the network (e.g. the use of antibiotics or 5-ASA), this meant that these studies could not be included in the network.

Quality of the evidence

Key to interpreting the results in such a network analysis is the consideration of the range of tools used to assess certainty, quality, and risk of bias. Adalimumab was included in just two studies in the network, with 26 participants receiving the intervention. The certainty of the evidence was thus low due to very serious imprecision and risk of bias, a key issue that limits the evidence for this intervention. Conversely, the ranking for 5-ASA, as the only other therapy effective for preventing clinical relapse in the network, was based on eight studies (1124 participants), therefore the certainty of the evidence was not affected by imprecision, and was downgraded only once due to high risk of bias.

Only four out of 26 studies included in the three networks were at low risk of bias. This was mostly due to lack of blinding (performance and detection bias). Allocation concealment was unclear for most studies as well. We found that most of the comparisons were made between active interventions and reference comparator, with only five studies comparing active treatments only. This resulted in a poorly connected network. For the number of treatments that were assessed, the number of included studies may have been insufficient and inadequately powered, giving rise to imprecision across all three networks. Some of the contrasts across all three networks had some degree of inconsistency. Incoherence was noted in the endoscopic relapse and withdrawal due to adverse events networks, albeit insufficient to warrant downgrading. We cannot rule out the possibility of publication bias resulting from small-study effects in the three small studies on adalimumab. Given the ranking and apparent efficacy of adalimumab, assessment for publication bias is key. However, given the low number of studies published, an accurate consideration of this is not permitted until further studies are published. We found no evidence of publication bias in any of the networks. By following strict inclusion criteria, we were able to avoid indirectness and did not downgrade the evidence for it.

Potential biases in the review process

There were a number of studies that reported sufficient data but were excluded from the network. We are aware of the fact that this could amount to reporting bias, and it did reduce the volume of evidence, giving rise to imprecision. However, the exclusion of such studies was based on advice from clinician authors, as participants were given active interventions to which they were not

randomised to receive. Due to clinical differences in interventions between studies in the same contrast, the decision was made to exclude these studies and avoid transitivity. The studies are still included in the review for completeness. In summarising the evidence, we focused on the best five treatments in clinical relapse and performance with other outcomes. The decision to disregard the worst five treatments was based on the fact that whilst these treatments are used capriciously without efficacy, the top five treatments have been studied in separate reviews where they have been shown to be efficacious.

We initially planned to evaluate clinical relapse and withdrawal due to adverse events. However, when the draft NICE guideline was completed (NICE 2019), we decided to include endoscopic relapse in the summary of evidence. This was solely to ensure consistency, given that this review and the NICE guideline are addressing the same question using a similar evidence base and methods.

Decisions on which interventions to include in the base case, lumping and splitting, as well as sensitivity analysis were made independently by two clinician authors who had no access to the data at that point in time.

Agreements and disagreements with other studies or reviews

Several guidelines on the maintenance of surgically induced remission in Crohn's disease have been published by European Crohn's and Colitis Organisation (ECCO), the American College of Gastroenterology, and the National Institute of Health and Care Excellence (NICE). Only the NICE guideline used an NMA methodology (NICE 2019). As discussed in the Background, there are small but stark differences in inclusion criteria, methodology, and most importantly decision-making processes between this Cochrane Review and the NICE guidance in the UK. The NICE guideline process meant that whilst there was agreement on the best-ranking treatment for both clinical and endoscopic maintenance of remission (adalimumab) between the two reviews, NICE did not recommend the use of adalimumab based on cost-effectiveness. The same conclusion was made in this review, but it was based on low-certainty evidence for the network rather than cost. There were differences in how the certainty of the evidence was judged in the two reviews. This review is aligned with the *Cochrane Handbook for Systematic Reviews of Interventions* and associated guidance (Higgins 2011), but whilst our review has rated the network as low certainty, the NICE guidance has arrived at a moderate rating (completed as per the NICE methodological guidance).

The NICE guideline recommends azathioprine with or without metronidazole, which is in disagreement with our review. This was due to a key difference between the two systematic reviews. It has been noted that several included studies that exerted influence on the network included participants who received non-randomised active agents, specifically metronidazole. However, metronidazole has been studied as a primary active interventional agent within this context. As such, we did not believe it was appropriate to include these studies in the network because this does not meet the transitivity assumptions for NMA and therefore limits the conclusions that can be made from the NICE meta-analysis.

Our review assessed azathioprine and 6-MP together as purine analogues and did not find clear evidence of effectiveness for either clinical or endoscopic maintenance of remission. Given that it included a number of extra studies that used purine analogues with concomitant metronidazole, the NICE review arrived at a different conclusion, recommending this combination as primary therapy. This was not consistent with the findings of our review.

5-aminosalicylic acid was found to be safe and beneficial for preventing clinical relapse and was recommended in the 2012 NICE guideline. However, this recommendation was removed from the update guideline, stating that 5-ASA had not been shown to be clinically or cost-effective in terms of endoscopic relapse rates (NICE 2019). This was not consistent with the findings of our review. This difference in findings was due to the exclusion of a number of studies, which was the result of the difference in inclusion criteria (Florent 1996; Herfarth 2006; Reinisch 2010; Sutherland 1997). We permitted the inclusion of abstract publications and studies with less than 12 months' follow-up. Interestingly, one of the recommendations for future research within this NICE guideline was for studies assessing 5-ASA compared to no treatment. Based on our findings of moderate-certainty evidence supporting the effectiveness of 5-ASA when compared to placebo, this is another area of disagreement with the NICE guideline, and further research in this area may not be warranted.

The European Crohn's and Colitis Organisation (ECCO) released an update to their international guidance on Crohn's management in 2017, which covered postsurgical treatment to maintain remission (Gionchetti 2017). Their recommendation 8G states: "Prophylactic treatment is recommended after ileocolonic intestinal resection in patients with at least one risk factor for recurrence [EL2]. To prevent post-operative recurrence the drugs of choice are thiopurines [EL2] or anti-TNFs [EL2]. High dose mesalazine is an option for patients with an isolated ileal resection [EL2]. Imidazole antibiotics have been shown to be effective after ileocolic resection but are less well tolerated [EL1]". The findings of our review would not fully support this current advice. The evidence does not support the use of thiopurines and does raise some specific safety issues that are not mentioned in this guidance, namely the occurrence of pancreatitis (leukopenia is mentioned). The evidence does support the use of one specific ant-TNF, but within the limitations noted. There is evidence to support the advice for 5-ASA in all patients. However, we found no evidence to support the use of antibiotics.

The American College of Gastroenterology released updated guidelines in 2018, which also address this issue (Lichtenstein 2018). These are as follows.

Recomendation 55 states: "Mesalamine is of limited benefit in

preventing postoperative Crohn's disease, but in addition to no treatment is an option for patients with an isolated ileal resection and no risk factors for recurrence (moderate level of evidence)". This agrees with the findings of this review.

However, recommendation 56 states: "Imidazole antibiotics (metronidazole and ornidazole) at doses between 1 and 2 g/day can be used after small intestinal resection in Crohn's disease patients to prevent recurrence (conditional recommendation, low level of evidence)". This was not completely supported by our findings, although the conditional nature of the recommendation and its associated GRADE rating was noted.

Similarly, recommendation 57 states: "Thiopurines may be used to prevent clinical and endoscopic recurrence and are more effective than mesalamine or placebo. However, they are not effective at preventing severe endoscopic recurrence (strong recommendation, moderate level of evidence)". Our findings do not support this. This recommendation cites the results of an out-of-date Cochrane Review and does not cite our last review of thiopurines (Gjuladin-Hellon 2019b).

Finally, recommendation 58 states: "In high-risk patients, anti-TNF agents should be started within four weeks of surgery in order to prevent postoperative Crohn's disease recurrence (conditional recommendation, low level of evidence)". This agrees with our findings.

AUTHORS' CONCLUSIONS

Implications for practice

We were unable to draw conclusions on which treatment is most effective in preventing clinical relapse and endoscopic relapse because the certainty of the evidence for the networks was either low or very low. Our review found some evidence indicating that adalimumab and 5-aminosalicylic acid (5-ASA) may prevent clinical relapse. Budesonide may not be effective in preventing clinical relapse, thus may not be useful in practice for the purpose of maintaining surgically induced remission. These findings must be considered in the context of the low certainty of the evidence of the network. There is insufficient evidence to determine which treatment is safest or most effective in preventing endoscopic relapse, as the certainty of evidence was very low. Whilst safety advice is well recognised for thiopurines, the finding of a higher number of cases of pancreatitis is worth noting.

Implications for research

The need for future research must be grounded in the current evidence base synthesised within this network. Given the widespread use of both adalimumab and infliximab in medically induced maintenance therapy and the results within the network, both treatments require further research. Such trials may consider multiple trial arms including both placebo and other 'standard' therapies, such as 5-ASA. Similarly, given the lack of evidence to support the use of thiopurines despite their widespread use and recognition in international guidelines, future research involving these agents is clearly key. Placebo trials are not needed, rather trials comparing with either biologic or 5-ASA therapy may have the most utility. Whilst other agents may need researching, these would not currently be priorities.

The design of such studies is key. We would highly recommend that researcher consider the core set of outcome measures recently proposed (Kim 2017). Additionally, longer follow-up will be of significant benefit for clinicians interpreting results with clearer reporting on withdrawals from study.

The issue of sample size must be highlighted. Many of the studies included in this review were very small. We would strongly advise the use of indicative odds ratios from this review when performing power calculations. Such accurate calculations are vital to halt the large number of low-powered studies and include the precision of findings.

In terms of study design, allocation concealment and blind outcome assessment were major sources of bias in the review, which should be improved on in future trials. There is also a need for better outcome reporting, in particular adverse events, which will provide a much needed understanding of the safety of these interventions.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ardizzone 2004

Methods	**Study design:** RCT, single centre **Setting:** University "L.Sacco" Hospital (Milan, Italy), 1994 to 2001
Participants	**Inclusion:** Adult (18 to 70 years) participants who underwent surgery for symptomatic intestinal stenosis or occlusion, which is clinically quiescent (CDAI $\leq$ 150); able to start oral nutrition and oral medication within the first 2 postoperative weeks **Exclusion:** Contraindications for use of MES or AZA and pre-existing hepatic disease, renal dysfunction, clinically important lung disease, systemic infection, short-bowel syndrome, presence of alcoholic stoma, history of cancer, hypersensitivity to MES or AZA, erythrocyte macrocytosis, use of immunosuppressive drugs in the past 3 months; patients who had received treatment with anti-TNF-α within 6 months before surgery; pregnancy/breastfeeding; patients who had undergone surgical procedures other than conservative surgery or for perianal disease only; history of corticosteroid-dependent disease **Age (IG1/IG2) mean:** 38.4 years mean overall **Sex (M:F):** 95:52 overall; (45:26) vs (50:26) **Type of surgery:** Stricturoplasty 36; minimal bowel resection 70; minimal bowel resection stricturoplasty 36 **Previous surgery (IG1 + IG2):** 69/142 overall (38/71) vs (31/71) **Start of intervention after surgery:** < 2 weeks **Medication use (IG1 + IG2):** MES or sulfasalazine 62; corticosteroids 41; immunosuppressants 9; none 30 **Smoker (IG1/IG2):** (28/71) vs (36/71) **Number randomised (n = 142):** 71 vs 71 **Number analysed (n = 138):** (69/71) vs (69/71) (ITT); 50/71 vs 61/71 (per protocol) **Postrandomisation exclusion (n = 11)**: (6/71) vs (5/71) (did not start the treatment (3) (2 vs 1); lost to follow-up (8) (4 vs 4))
Interventions	**Group 1:** AZA administered at a dosage of 2 mg/kg/day **Group 2:** MES was administered at a dosage of 3 g/day divided into 3 doses **All participants:** Treatment with aminosalicylates, metronidazole, and any other CD-specific treatment had to be discontinued. Corticosteroids were allowed to be tapered by standardised stepwise dose reductions within 6 weeks after surgery at the latest. Symptomatic treatment with antacids, antidiarrhoeal agents, or spasmolytic agents was allowed but had to be scrupulously recorded. Compliance with treatment was evaluated by a simple questionnaire in which adverse events were also recorded. Participants receiving AZA were regularly assessed by total blood cell count and serum transaminase values to monitor any myelotoxicity and hepatotoxicity of the treatment. Participants were seen at baseline and every 6 months
Outcomes	**Duration of study:** 24 months 1. **Clinical relapse** defined as the presence of symptoms related to CD, variably associated with radiologic, endoscopic, and laboratory findings, with a CDAI score > 200, which is considered severe enough to warrant treatment with a systemic corticosteroid at a

	medium-high dose 2.**Surgical relapse** defined as the presence of symptoms refractory to medical treatment or complications requiring another surgical procedure (e.g. occlusive disease, intra-abdominal abscesses, or high-flow fistulas) 3.**Adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Sample size:** Based on a maximum relapse rate at 2 years of 45% MES, 62 participants per treatment group was considered sufficient to detect a difference of ≥ 25% for the AZA treatment group (type 1 error of 5%). The number of participants in each group was increased to 68 to compensate for an anticipated dropout rate of 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After surgery, participants who met the inclusion criteria and who agreed to enter the study were randomised to receive mesalamine or AZA by a computer-generated list" and "Randomization was performed in blocks of 10" Comment: computer-generated block randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the study is open-label and blinding is not performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement, however it is unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "In the intention-to-treat analysis, all randomised participants who received at least one dose of the study drug and were subjected to the baseline evaluation were considered for the analysis." and "Outcome measures were analysed in all randomised participants who had taken at least one dose of the study medication (intention-to-treat population)…" Comment: withdrawals were low and balanced across groups

Ardizzone 2004 (*Continued*)

Selective reporting (reporting bias)	Low risk	Trial registration not available, however, all outcomes stated in the method section were assessed and reported
Other bias	Low risk	Quote: "No significant differences were observed between the 2 treatment groups regarding age, sex, duration of disease, location of disease, fistula and abscess at surgery, surgical procedure, previous operations, and CD therapy during the previous 6 months" Comment: baseline characteristics well balanced across groups
All domain risk of bias	Unclear risk	High

Armuzzi 2013

Methods	**Study design:** RCT, single centre **Setting:** Italy, 2007 to 2011
Participants	**Inclusion:** Consecutive CD participants who underwent curative ileocolonic resection (all macroscopically inflamed tissues were removed and operative margins were disease-free at histopathology examination) and considered at "high risk" of postoperative recurrence were enrolled **Exclusion:** 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 leukopenia (WBC < 3000 μU/mL, lymphocyte count < 1000 μU/mL), and pregnancy **Age (IG1/IG2) median (range):** 32 (18 to 70) overall **Sex (M:F):** 15:7 overall; (7:4) vs (8:3) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** 2 to 4 weeks **Medication use (IG1 + IG2):** Previous treatment with AZA-5; previous treatment with IFX -10 **Smoker (IG1/IG2):** Not reported **Number randomised (n = 22):** 11/11 **Number analysed (n = 22):** (11/11) vs (11/11) **Postrandomisation exclusion (n = 0)**
Interventions	**Group 1:** Infliximab (5 mg/kg) at 0, 2, and 6 weeks and then every 8 weeks for 1 year **Group 2:** Azathioprine (2.5 mg/kg/day) for 1 year **All participants:** All participants also received oral metronidazole (500 mg twice daily) for 2 weeks after surgery. No other CD-related drugs were admitted during the study. Participants were evaluated monthly, according to laboratory tests, the Harvey-Bradshaw Index (HBI) calculation, and the adverse event report

Armuzzi 2013 (*Continued*)

Outcomes	**Duration of study:** 12 months and follow-up at 40 months 1.**Clinical recurrence** defined by a HBI $\geq$ 8 2. **Endoscopic recurrence** defined by a Rutgeerts' score $\geq$ i2 at 12 months and 40 months (follow-up) 3. **Histologic activity score** based on a Histology Score System modified from Regueiro and colleagues 4. **Adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Authors declare the following conflict of interest: AA received: consultancy from Abbvie, MSD; lecture fees from Abbvie, MSD, Chiesi, Ferring, Nycomed, Otsuka; educational grants from Abbvie, MSD, Ferring, Nycomed. LG received: educational grants from Abbvie, MSD. CF, AP, MM, DP, GA, FF, IDV, GLR: nothing to declare

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomised with a simple unblinded 1:1 allocation ratio to receive…" Comment: simple randomisation performed, however insufficient information on the method of randomisation used
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "One unblinded endoscopist (AP) did all the examinations and calculated scores. Two further unblinded endoscopists (IDV and GA) separately reviewed videos and in case of discordance a consensus agreement was reached among the three operators." Comment: blinding of outcome assessors not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient did not tolerate azathioprine because of severe nausea with epigastric pain and withdrew from the study after 5 weeks of treatment" Comment: only one participant withdrew from the study and reason described

Armuzzi 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcome data stated in the method section were reported.
Other bias	Low risk	Groups well balanced at baseline and no other apparent sources of bias detected
All domain risk of bias	High risk	Very high

Bergman 1976

Methods	**Study design:** RCT, multicentre **Setting:** Sweden/University Hospital Upsala, Country hospitals in Vastergas, Gavle and Falun, 1969 to 1972
Participants	**Inclusion:** Participants with a true path-anatomical diagnosis of CD who had undergone macroscopically and microscopically radical resection of the gut in the mentioned hospitals between September 1969 and April 1972 **Exclusion:** Salazopyrin intolerance, patients unable to follow given instructions for the medical therapy **Age (IG1/IG2) median:** Not reported; 28 years overall **Sex (M:F):** Not reported (reported for those 84 who completed the study: (20:29) vs (18:17)) **Type of surgery:** Primary radical resection (70) **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** 7 to 8 days **Medication use (IG1 + IG2):** Previous treatment with AZA-5; previous treatment with INF -10 **Smoker (IG1/IG2):** Not reported **Number randomised (n = 97):** 57/40 **Number analysed (n = 84):** (49/57) vs (35/40) **Postrandomisation exclusion (n = 13)**: (8/57) vs (5/40) (reasons not reported)
Interventions	**Group 1:** Combination of sulfasalazine (Salazopyrin) and corticosteroids for 33 weeks. Salazopyrin tablets were administered in a dose of 3 g daily for 16 weeks, and then 1.5 g daily for 17 weeks. Prednisolone tablets were given 15 mg daily from the 7th to 8th postoperative day for 2 weeks, then 10 mg daily for 14 weeks, and 5 mg daily for the last 17 weeks **Group 2:** No treatment **All participants:** During the first postoperative year, all participants were checked up in the outpatient clinics at the time of changing medical treatment. Participants were followed up until 3 years after operation. Participants were seen at least once a year, and at least once a year (and when necessary) an X-ray was performed
Outcomes	**Duration of study:** 33 weeks 1.**Recurrence** based on typical roentgenologic findings for CD (*reported ≤ 1, $> 1 \leq 2$, and $> 2 \leq 3$ years)

Bergman 1976 (*Continued*)

Notes	**Funding source:** Supported by the Swedish Medical Research Council **Conflict of interest:** Not reported **Power calculation**: Not reported *Data from > 1 ≤ 2 and > 2 ≤ 3 years not included in analysis as treatment duration was 33 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "..groups assigned by drawing a lot" Comment: simple randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Insufficient information provided, but blinding very unlikely
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "All the X-rays were scrutinised by a radiologist at the University Hospital in Upsala. The repeated examinations performed during the postoperative observation years made it easier to diagnose a recurrence" Comment: insufficient information provided, however it is unlikely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates were low and balanced across groups, however reasons were not reported
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.
Other bias	High risk	Baseline characteristics not provided. Imbalance in numbers randomised (40 vs 57)
All domain risk of bias	High risk	Very high

Brignola 1995

Methods	**Study design:** RCT, multicentre **Setting:** Italy, 8 centres, 1990 to 1992 enrolment
Participants	**Inclusion:** Patients with so-called curative resection, such as those who have undergone removal of all macroscopic disease in the ileal or ileocaecal region **Exclusion:** Patients with localisation of CD in another region or having resection of >

Brignola 1995 (*Continued*)

	100 cm were excluded **Age (IG1/IG2) mean (SD):** 36.5 ± 14 overall; (39 ± 17) vs (34 ± 10) **Sex (M:F):** 42:45 overall; (22:22) vs (20:23) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 24 overall; (13/44) vs (11/43) **Start of intervention after surgery:** ≤ 1 month **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** 44 overall (22/44) vs (22/43) **Number randomised (n = 87):** 44/43 **Number analysed (n = 85):** (43/44) vs (42/43) **Postrandomisation exclusion (n = 10)**: (6/44) vs (4/43) (side effects 8 (5/3); lost to follow-up 1 (1/0); protocol violation 1 (0/1)
Interventions	**Group 1:** MES tablets 3 g/day for 12 months (2 tablets Pentasa (500 mg) 3 times a day) **Group 2:** Identical placebo tablets **All participants:** Laboratory tests performed at baseline after 1 month and then every 3 months for evaluation of haematologic, renal, and hepatic function
Outcomes	**Duration of study:** 12 months 1.**Clinical recurrence** defined as worsening of symptoms by at least 100 CDAI points above the level at the previous visit and attainment of a CDAI score of more than 150 2. **Endoscopic recurrence** based on a standardised form for description of endoscopic lesions by type (aphthous lesion, large ulcer, nodule, or narrowing) and characteristics (number, size, and whether a diffuse or skip lesion) 3. **Severe endoscopic recurrences** (i score of 3 and 4) 4.**Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Sample size**: The severe endoscopic recurrence (score 3 to 4) rate in the placebo group was estimated to be 50%. The decision was made to enrol 80 participants (40 per group) to detect a significant difference in comparison with the active group (30% recurrence) (1-tailed test; α level, 5%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Each center received material for at least 4 cases labelled with a patient code number according to a randomisation made in balanced blocks" Comment: block random sequence generation, but method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "Each center received material for at least 4 cases labelled with a patient code number according to a randomisation made in balanced blocks"

Brignola 1995 (*Continued*)

		Comment: unclear whether drug containers were identical. Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The treatment blinding code was broken in September 1993 when all the assessments were finished; no serious adverse event necessitated breaking of the code beforehand" Comment: double-blind trial, participants received placebo tablets that were identical to the study intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endoscopists, unaware of the treatment that the patient had received, recorded on a standardized form a description of endoscopic lesions by type...At the end of the trial, two investigators not previously involved in the patients' follow-up and unaware of which treatment the patients had received and also of the overall assessments provided by each center, independently evaluated all of the standardized forms with a description of endoscopic and radiological responses; their assessments were then compared with those furnished by the investigators from the original center...The treatment blinding code was broken in September 1993 when all the assessments were finished; no serious adverse event necessitated breaking of the code beforehand" Comment: blinding maintained until after assessments were finished
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were low and balanced across groups with reasons reported
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "Clinical characteristics that were considered in our trial were well balanced between the mesalamine group and the placebo" Comment: groups well balanced at baseline. No other apparent biases

Brignola 1995 (*Continued*)

All domain risk of bias	Low risk	Low/unclear

Caprilli 1994

Methods	**Study design:** RCT, multicentre **Setting:** Italy, 15 collaborating centres, 1990 to 1992 enrolment
Participants	**Inclusion:** 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:** Localisation of the disease to the jejunum, proximal ileum, left colon, or ano-rectum; known side effects from sulfasalazine or salicylates; severe diseases unrelated to Crohn's disease (e.g. renal or liver dysfunction); treatment with drugs that may alter intestinal pH (H,-receptor antagonists, omeprazole); pregnancy; questionable ability to co-operate and give consent **Age (IG1/IG2) mean (range):** 35.5 (16 to 61) vs 33.7 (16 to 58) **Sex (M:F):** 55:40 overall; (32:15) vs (23:25) **Type of surgery:** Elective 71; emergency 24 **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** $\leq$ 2 weeks **Medication use (IG1 + IG2):** MES 46; corticosteroids 59; metronidazole 25; sulfasalazine 21 **Smoker (IG1/IG2):** Not reported **Number randomised (n = 110):** 55/55 **Number analysed (n = 95):** (47/55) vs (48/55) **Postrandomisation exclusion (n = 17)**: (9/55) vs (8/55) (randomised, no endoscopy at base 15 (8/7); dropout 2 (1/1)
Interventions	**Group 1:** 2.4 g/day of Eudragit-S coated MES **Group 2:** No treatment **All participants:** Participants were seen for clinical and laboratory assessment at 2 weeks after surgery, at 3, 6, and 12 months, and annually thereafter. Colon-ileoscopy was performed at 6 and 12 months, and annually thereafter. Clinical, laboratory, and endoscopic examinations were brought forward if symptoms recurred. Participants requiring corticosteroids or surgery were withdrawn from the study. Participants who stopped the treatment for more than 2 weeks or who presented with severe side effects were considered to be dropouts. Adverse events and reported compliance with the drug were recorded at each visit
Outcomes	**Duration of study:** 24 months 1. **Recurrence** defined as the presence of typical endoscopic Crohn's disease lesions in the neoterminal ileum or anastomosis, or both according to the criteria proposed by Rutgeerts and colleagues (judged as no, mild, or severe) 2. **Adverse events** (skin rash, epigastric pain, nausea, vomiting) 3. **Withdrawal due to adverse events**

Notes	**Funding source:** Supported in part by Bracco SpA (Milan) **Conflict of interest:** Not reported **Sample size**: The study enrolled 55 consecutive participants in each arm of the trial, which was sufficient to demonstrate a fall in the recurrence rate from 90% to 80% with a power of 0.90 and a 0.05 one-sided type I error. Only the 95 participants with almost 6 months of observation were considered in the statistical analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly allocated to receive 2.4 g/day of Eudragit-S coated mesalazine (Asacol, Bracco SPA, Italy) or no treatment at all" Comment: insufficient information on random sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This multicentre study was not blind" Comment: open-label study design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "On the first occasion, the endoscopist was unaware of the treatment; on the second, the tapes were shown with a different sequence and the endoscopist was informed of treatment... The variability sources of the recurrence classification were evaluated... However, the results of the reliability study suggest that lack of blindness in the endoscopists collaborating on the trial was no relevant. In fact, we found that the endoscopists were not in disagreement in the assessment of recurrence nor was the diagnosis of recurrence affected by endoscopists' awareness of the kind of treatment" Comment: there was some form of blind outcome assessment, and the reliability study comparing blind vs unblind assessment showed that lack of blinding had no effect on outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The cumulative proportions of symptomatic recurrence and asymptomatic recurrence were estimated by the lifetable

		method on the intention-to-treat principle" Comment: attrition rate was low and balanced across groups
Selective reporting (reporting bias)	Low risk	All outcome data stated in the methods section were reported
Other bias	Low risk	Quote: "the groups were homogenous for age, duration of the disease, site and extent of the lesions, clinical course perforating or non-perforating), previous treatment, indication and type of surgery, and CDAI score at operation. Males more common in MEZ group" Comment: groups well balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	Unclear risk	High

Caprilli 2003

Methods	**Study design:** RCT, multicentre **Setting:** Italy, 17 collaborating centres, enrolment 1997 to 2000
Participants	**Inclusion:** Adults (18 to 65 years) with CD limited to the terminal ileum (lesions not exceeding 1 m), with or without involvement of the caecum/ascending colon, evaluated by colonoscopy and small bowel follow-through within 1 month before surgery; 1st or 2nd resection, and considered by the surgeon during the operation to be 'radical' (complete removal of the macroscopically involved intestinal segment); absence of skip lesions; diagnosis of CD confirmed macroscopically and microscopically by standard criteria **Exclusion:** Localisation of the disease to the jejunum, proximal ileum, transverse colon, left colon, or ano-rectum; small bowel resection exceeding 1 m; known side effects from sulfasalazine or salicylates; severe diseases unrelated to Crohn's disease (e.g. renal or liver dysfunction); treatment with drugs likely to affect intestinal pH; pregnancy; questionable ability to co-operate; inability to give informed consent **Age (IG1/IG2) mean:** 33.8 vs 36.4; overall age not reported **Sex (M:F):** 114:93 overall; (49:52) vs (64/41) **Type of surgery:** Emergency 45; elective 161 **Previous surgery (IG1 + IG2):** First 166; second 40 **Start of intervention after surgery:** $\leq$ 2 weeks **Medication use (IG1 + IG2):** MES 153; steroids 123; antibiotics 71; immunosuppressants 20 **Smoker (IG1/IG2):** (21/ 101) vs (27/105) **Number randomised (n = 206):** 101/105 **Number analysed (n = 202):** (99/101) vs (103/105)

	Postrandomisation exclusion (n = 61): Withdrawals from clinical control (n = 20) (6 vs 14); withdrawals from endoscopy (n = 41) (17 vs 24)
Interventions	**Group 1:** 4.0 g/day of oral Eudragit-S-coated MES (Asacol). Participants received 5 tablets of MES (800 mg) divided into 3 doses (1 + 2 + 2 tablets) **Group 2:** 2.4 g/day of oral Eudragit-S-coated MES (Asacol). Participants received 3 tablets of MES (800 mg) divided into 3 doses (1 + 1 + 1 tablets) plus 2 tablets of placebo identical in appearance **All participants:** No other pharmacological treatment was given, with the exception of antidiarrhoeal drugs on demand. Participants were seen for clinical and laboratory assessment 2 weeks after surgery, and then at 6 and 12 months. Colon ileoscopy was performed at 12 months. Clinical, laboratory, and endoscopic examinations were brought forward if recurrence of symptoms was reported before the scheduled follow-up. Adverse events and reported compliance with the drug were recorded at each visit
Outcomes	**Duration of study:** 12 months 1. **Endoscopic recurrence** defined as the presence of typical endoscopic CD lesions in the neoterminal ileum or anastomosis, or both, and was graded according to the criteria of Rutgeerts and colleagues. 3 different degrees of endoscopic recurrence were evaluated: (i) an endoscopic score of > 0; (ii) an endoscopic score of > 1; and (iii) an endoscopic score of > 2 (severe recurrence) 2. **Clinical recurrence** defined as CDAI > 150 points or an increase in CDAI score of > 100 points 3.**Adverse events** 4. **Withdrawals due to adverse events**
Notes	**Funding source:** Supported by a grant from Giuliani SpA, Milan, Italy **Conflict of interest:** Not reported **Sample size**: Assuming that 2.4 g/day MES would reduce severe endoscopic recurrence from 70% to 55% at 1 year of follow-up, it was hypothesised that 4.0 g/day MES would reduce the rate of severe endoscopic recurrence to 30%. The number of participants needed to ensure a type 1 and type 2 error level of 5% calculated was 85 participants per group plus 25% dropouts (i.e. a further 43 participants). The total number of participants required was therefore 213

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in blocks of four according to a computer-generated randomization scheme provided by an independent institution at the beginning of the trial and forwarded to the Department of Clinical Trials at Giuliani SpA" Comment: computer-generated randomisation

Caprilli 2003 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "...provided by an independent institution at the beginning of the trial and forwarded to the Department of Clinical Trials at Giuliani SpA" Comment: central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "All patients and investigators were blind with regard to treatment allocation" Comment: double-blinded RCT, but no explanation of how conditions of blinding were achieved. Given the variation in doses between study groups (5 vs 3 tablets) , blinding is unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatment blinding code was broken in June 2000 when all assessments had been completed" Comment: assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Outcome measures were analysed in all randomized patients who had taken at least one dose of the study medication (intention-to-treat population)" Comment: attrition rates were similarly low and balanced across groups, except for the endoscopy outcome where attrition rates were about 20%
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated at the methods section were reported adequately
Other bias	Low risk	Groups well balanced at baseline, compliance satisfactory; no other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Chermesh 2007

Methods	**Study design:** RCT, multicentre **Setting:** 4 medical centres in Israel, enrolment 1997 to 2000
Participants	**Inclusion:** CD participants undergoing resection in 1 of the medical centres affiliated with the study and who were eligible to take part according to their physician participated in the study **Exclusion:** not reported

	Age (IG1/IG2) mean (SD): 35.7 ± 12.2 overall; 36.1 ± 13.0 vs 34.7 ± 9.9 **Sex (M:F):** 23:7 overall; (15:5) vs (8:2) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** As soon as participants resumed oral intake after surgery **Medication use (IG1 + IG2):** 5-ASA 58; immunosuppressants 59; at least 1 course of steroids 60 **Smoker (IG1/IG2):** 10/30 overall; (8/20) vs (2/10) **Number randomised (n = 30):** 20/10 **Number analysed (n = 30):** (20/20) vs (10/10) **Postrandomisation exclusion (IG1/IG2) (n = 10)**: (6/20) vs (4/10); self-withdrawal 8 (5/3); pregnancy 2 (1/1)
Interventions	**Group 1:** 1 daily dose of Synbiotic 2000, which contains a mixture of prebiotics and probiotics **Group 2:** Placebo **All participants:** Treatment began as soon as participants resumed oral intake after surgery. All participants were treated with at least 1 course of steroids. Follow-up visits were scheduled at 0, 1, 2, and 3 months and every 3 months thereafter until 24 months postsurgery. Follow-up consisted of endoscopic, clinical, and laboratory parameters
Outcomes	**Duration of study:** 24 months 1. **Rutgeerts score** 2.**CDAI score**
Notes	**Funding source:** No funding; probiotics and placebo provided free of charge (via correspondence with authors 3 August 2018) **Conflict of interest:** Authors declare no conflict of interest (via correspondence with authors 3 August 2018) **Power calculation**: Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized to active treatment or placebo in a 2:1 ratio" Comment: insufficient information provided, however authors contacted on 3 August 2018 and indicated that randomisation was done manually at the medical centre
Allocation concealment (selection bias)	High risk	Insufficient information provided, however authors contacted and confirmed that "predefined notes with allocation were prepared, and for each patient a note with the treatment group allocation was drawn". We

		do not consider this sufficient to prevent bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was placebo-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was referred to as double-blinded, however there is insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Half of the randomised participants dropped out of the trial. This early discontinuation of the study was due to an interim analysis that found no benefit of the active treatment. We do not consider this a source of bias
Selective reporting (reporting bias)	High risk	Trial registration was not available. CDAI and Rutgeerts mean score were reported for the control group, but not for the active treatment group; instead they merely reported as 'NS' (not significant)
Other bias	Low risk	Quote: "No differences were found between the 2 treatment groups regarding gender, age at diagnosis, age at surgery, weight, smoking status, type of disease, length of resected segment, or medical treatment prior to surgery" Comment: groups balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	High risk	Very high

D'Haens 2008

Methods	**Study design:** RCT, multicentre **Setting:** Belgium/University Hospital Leuven and Imelda General Hospital, Bonheiden; 1999 to 2005
Participants	**Inclusion:** Adult participants (18 to 70 years) who underwent curative ileal or ileocolonic resection with ileocolonic anastomosis for CD with a presence of 1 risk factor for the development of early/severe postoperative recurrence of their CD. Participants had to understand and sign a written informed consent form. Women of childbearing age needed to have a negative pregnancy test and had to use adequate birth control measures during the whole study **Exclusion:** Presence of macroscopic evidence for CD proximally or distally to the site of resection or the presence of frank pancolitis or an ileorectal anastomosis (ileosigmoidal

	anastomosis was allowed); patients with a stoma; operation for fibrostenosis only, without evidence of inflammatory activity on histology; former intolerance to metronidazole or AZA or both; who wished to become pregnant; low white blood cell count at inclusion (4000); alcohol or drug abuse; use of AZA in the 2 months before surgery; patients with malignancies and/or ongoing infectious disease (hepatitis, tuberculosis, AIDS) with the exception of herpes simplex infection. Former use of biologicals was not permitted **Age (IG1/IG2) mean:** 38.8 (22 to 67) vs 40.0 (21 to 69); overall age not reported **Sex (M:F):** 44:37 overall; (24:16) vs (20:21) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 2nd surgery 20 (12/8); 3rd surgery 3 (2/1) **Start of intervention after surgery:** ≤ 2 weeks **Medication use (IG1 + IG2):** AZA past use: 5 (3/2); steroid use at surgery: 21 (12/9) **Smoker (IG1/IG2):** (13/40) vs (17/41) **Number randomised (n = 81):** 40/41 **Number analysed (n = 81):** (40/40) vs (41/41) **Postrandomisation exclusion (n = 5)**: (3/40) vs (2/41) (withdrawal of consent 5 (3/2))
Interventions	**Group 1:** 3 months of metronidazole therapy at a dose of 250 mg 3 times per day plus AZA depending on body weight. AZA only for the rest of the study. Participants whose body weight was under 60 kg received 2 tablets of AZA (100 mg), whereas participants weighing over 60 kg received 3 tablets or 150 mg AZA **Group 2:** 3 months of metronidazole therapy at a dose of 250 mg 3 times per day plus placebo. Placebo only for the rest of the study **All participants:** Participants intolerant to metronidazole were switched to ornidazole 500 mg twice per day orally. All concomitant anti-inflammatory 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. Colestyramine was allowed for the treatment of bile acid diarrhoea. Participants were instructed to take their other drugs at least 1 hour after the intake of colestyramine. Participants underwent clinical evaluation with physical examination and biochemical analysis at baseline and weeks 2, 6, 12, 20, 28, 36, 44, and 52 after randomisation. Participants underwent an ileocolonoscopy at week 12 and 52. Adverse events and concomitant medication were recorded at every scheduled or unscheduled visit
Outcomes	**Duration of study:** 12 months 1. **Endoscopic recurrence** in the neoterminal ileum defined as an endoscopic index ≥ 2 according to Rutgeerts' endoscopic score 2. **Clinical recurrence** defined as CDAI > 250 3.**Adverse events** 4. **Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: It was estimated on the basis of prior recurrence-prevention studies, that 50% to 55% of participants in the placebo group would have an endoscopic recurrence at 1 year. Assuming an efficacy of 65% of AZA, it was calculated that 80 participants would need to be enrolled in the trial to detect differences in significant endoscopic recurrence amongst the groups

D'Haens 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The random allocation sequence was delivered by a randomization program written in Visual Basic version 6" Comment: computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization took place in the pharmacy of the Leuven University Hospitals within 2 weeks after surgery" Comment: insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Dummy tablets used, study was single-blinded. It is unclear whether personnel were blinded or not
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "At week 12 and 52, an ileocolonoscopy was performed with determination of Rutgeerts' score for ileal recurrence of CD by an endoscopist who was unaware of treatment assignment" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Both intention-to treat and per-protocol analyses were performed" Comment: ITT analysis applied, and attrition rates were similarly low across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were adequately reported
Other bias	Low risk	Quote: "The characteristics of the study populations in the AZA and placebo group were comparable'" Comment: groups well balanced at baseline, no other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Ewe 1989

Methods	**Study design:** RCT, multicentre **Setting:** Germany/16 surgical and medical centres; study period not reported
Participants	**Inclusion:** Adult participants resected for CD by 1 of the medical centres; resection had to be curative with no macroscopically inflamed intestine left; diagnosis of CD had to be confirmed macro- and microscopically **Exclusion:** Patients not resected according to the standard policy of the individual (radical or non-radical) operating centre; inability/refusal to give written consent; questionable ability to co-operate; age less than 18 years **Age (IG1/IG2) median (range):** 31 (15 to 66) overall; 32 (16 to 66) vs 30 (15 to 62) **Sex (M:F):** 113:119 overall; (48:63) vs (65:56) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 94 (48/46) **Start of intervention after surgery:** Immediately postoperatively **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 232):** 111/121 **Number analysed (n = 206):** (101/101) vs (105/105) **Postrandomisation exclusion (n = 88)**: (47/111) vs (41/121) (non-co-operative 57 (31/26); technical 18 (8/10); medical 13 (8/5))
Interventions	**Group 1:** Sulfasalazine 3 g daily for 3 years **Group 2:** Similar placebo (size, colour, form) **All participants:** Medication initiated whilst in hospital. Control visits at 3 months and every 6 months thereafter. Colonoscopy not obligatory, although encouraged
Outcomes	**Duration of study:** 3 years 1. **Recurrence of CD** proven by radiology, endoscopy, or operation (> 3 months, > 1 year, > 2 years, 3 years)
Notes	**Funding source:** Supported by Deutsche Forschungsgemeinschaft grant Ew 4/12,14, 16/1-3 **Conflict of interest:** Not reported **Power calculation**: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Yes, we carried out random allocation. We got the key from our statistical department" Comment: whilst the medical treatment part of the study is reported as randomised and double-blind, there was no further information on this in the trial. However, based on correspondence on 11 October 2018 with the lead author (Professor Ewe) , we conclude that random allocation was

Ewe 1989 (*Continued*)

		probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medical treatment part of the study is reported as randomised and double-blind. Dummy tablet similar to sulfasalazine was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote "Yes, the people who assessed the outcomes were aware of the intervention patients were allocated to" Comment: confirmed via correspondence on 11 October 2018 with the lead author (Professor Ewe)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition rate was around 37%, however compared to the event risk (60%) , it was not sufficient to introduce bias
Selective reporting (reporting bias)	High risk	Trial registration not available and adverse events outcome not reported
Other bias	Low risk	Baseline characteristics appear to be balanced across groups
All domain risk of bias	High risk	Very high

Ewe 1999

Methods	**Study design:** RCT, multicentre **Setting:** Germany/university hospitals in Heidelberg, Homburg, and Mainz; 1992 to 1994
Participants	**Inclusion:** Patients who have undergone curative resection for ileal, ileo-colonic, or colonic CD (i.e. without grossly visible disease at the resection margins) and had an anastomosis that was accessible to colonoscopy **Exclusion:** Not reported **Age (IG1/IG2) mean (SD):** 34 ± 10 overall; 35 ± 12 vs 33 ± 9 **Sex (M:F):** 37:46 overall; (21:22) vs (16:24) **Type of surgery:** Ileal resection or stricturoplasty 15 (8/7); ileo-caecal resection (right hemicolectomy) 49 (26/23); segmental colonic resection 11 (5/6); colectomy 4 (1/3) **Previous surgery (IG1 + IG2):** 52 (25/27) **Start of intervention after surgery:** ≤ 2 weeks **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 83):** 40/43 **Number analysed (n = 83):** (43/43) vs (40/40)

	Postrandomisation exclusion (n = 20): (11/43) vs (9/40) (non-compliance 20 (11/9))
Interventions	**Group 1:** 1 budesonide gelatine capsule 3 times daily before meals containing 1 mg of budesonide in approximately 400 microgranules 1 mm in diameter and coated for pH modified release with Eudragit L, which dissolves at pH > 6.4 **Group 2:** 1 placebo capsule indistinguishable from budesonide capsules 3 times daily before meals **All participants:** No other drugs used in the treatment of CD such as aminosalicylates, other glucocorticoids, or immunosuppressives were allowed. Preoperative treatment was stopped and in case of glucocorticoids was tapered to zero within 4 weeks. Participants were scheduled for the first visit 6 weeks after operation. Further visits were arranged at 3, 6, 9, and 12 months postoperatively. At each visit the clinical and blood status were obtained and symptoms and signs suggestive of budesonide side effects or of recurrence of CD were recorded
Outcomes	**Duration of study:** 12 months 1.**Endoscopic recurrence** graded according to a slightly modified scoring system based on Rutgeerts and colleagues (0, normal mucosa; 1, reddening and/or oedema without circumscribed lesions; 2, five aphthoid lesions within normal mucosa; 3, six aphthoid lesions within normal mucosa or isolated areas with greater ulcers; 4, diffusely inflamed mucosa containing aphthoid lesions or small ulcers; 5, diffuse inflammation with larger ulcers, pseudopolyps, and/or stenosis; an endoscopy score of 2 was defined as recurrence and treatment failure) 2. **Clinical recurrence** defined as rise in CDAI from 60 up to 200 from the first follow-up or a CDAI > 200. Symptoms and signs characteristic of CD were taken as recurrence in cases where colonoscopy was refused. (ITT derived from number of clinical relapses plus number with no available data.) 3.**Histologic recurrence** graded as follows: 0 = normal mucosa; 1 = scanty infiltration with lymphocytes and solitary neutrophils and eosinophils but more histiocytic infiltration of the lamina propria; crypt distortion; 2 = disturbed villous and crypt architecture; densely packed inflammatory cells; ulceration of surface epithelium; 3 = diffuse inflammation with inflammatory polyps; crypt distortion, crypt abscesses; lymphoid follicles in lamina propria 4.**Health-related quality of life** based on participants' global judgement (good; medium; bad) 5.**Adverse events** 6.**Severe adverse events** 7. **Withdrawal due to adverse even**t
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: A minimum sample size of 60 participants (30 per treatment group) was calculated by taking the following considerations into account: recurrence rate within 1 year under placebo 70% and under budesonide 35%. To compensate for dropouts, an overall sample size of 80 participants was agreed upon

Risk of bias

Bias	Authors' judgement	Support for judgement

Ewe 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "83 patients were randomized according to a computer-generated list" Comment: computer random number generator
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This study is a double-blind placebo-controlled clinical trial involving three university-based medical centres [...] Placebo medication was indistinguishable from budesonide" Comment: placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All biopsies were evaluated independently by the pathologists at the three study centres and uncertain diagnoses were discussed at a joint meeting" Comment: the study was reportedly double-blinded, however there is insufficient information to determine whether the pathologists were aware of the interventions to which participants were allocated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Calculations were performed based on all patients with Crohn's disease who had been operated on as outlined above and had taken the study medication for at least 1 day (intention-to-treat)" Comment: ITT was performed. However, over 20% of participants were withdrawn from the study, and there is insufficient information to determine how this compares with the event risk
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "Both groups were comparable with regard to their demographic and disease characteristics" Comment: both groups well balanced at baseline
All domain risk of bias	Low risk	Low/unclear

Fedorak 2015

Methods	**Study design:** RCT (phase 1), multicentre **Setting:** Canada/17 tertiary inflammatory bowel disease university-associated centres; 2003 to 2007
Participants	**Inclusion:** 16 years of age or older with a radiologic, endoscopic, or surgical diagnosis of Crohn's disease of at least 3 months duration. Patients who underwent resection of ileocolonic Crohn's disease at the physician's discretion, with margins macroscopically free of disease, and small bowel-to-colon anastomosis no more than 30 days before randomisation **Exclusion:** Patients with residual luminal disease; receiving a TNF antagonist within 8 weeks of resection **Age (IG1/IG2) mean (SD):** 36.7 ± 12.1 overall; 37.6 ± 12.4 vs 35.91 ± 1.8 **Sex (M:F):** 62:58 overall; (30:28) vs (32:30) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 1st 35 (20/15); 2nd 8 (4/4) **Start of intervention after surgery:** ≤ 2 weeks **Medication use (IG1 + IG2):** Prior MES use 96 (47/49); prior corticosteroid use 101 (50/51); prior immune modifier agents 64 (29/35); prior infliximab use 16 (7/9) **Smoker (IG1/IG2):** 32 total; (13/58) vs (19/62) **Number randomised (n = 120):** 58/62 **Number analysed (n = 120):** (58/58) vs (62/62) **Postrandomisation exclusion (n = 15)**: (10/58) vs (5/62) (withdrew consent 8; lost to follow-up 3; non-compliance 3; other 1)
Interventions	**Group 1:** 1 sachet of VSL#3 (a mixture of 8 different bacteria, 900 billion/sachet) twice daily for 3 months **Group 2:** Placebo identical sachets containing 3 g cornstarch for 3 months **All participants:** After resection, treatment of Crohn's disease was not permitted. Codeine, loperamide, diphenoxylate, and colestyramine were allowed for diarrhoea. Participants were reviewed at days 30 and 90. Telephone contacts occurred on days 14 and 60. At each visit a physical exam and medication adherence check were performed, and CDAI and IBDQ were calculated. At day 90, participants underwent a colonoscopy to evaluate endoscopic recurrence according to the Rutgeerts score
Outcomes	**Duration of study:** 3 months 1. **Endoscopic recurrence** defined as Rutgeerts score ≥ 1 2.**Severe endoscopic relapse** defined as Rutgeerts score ≥ 3 3.**Adverse events** 4.**Serious adverse events** 5. **Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: Under the assumption that the rate of severe endoscopic recurrence in placebo-treated participants would be 45%, 52 evaluable participants per group were required to detect an absolute difference of 25% (i.e. 20% rate of severe endoscopic recurrence in participants treated with VSL#3) at the .05 level of significance with 80% power. Consequently, a total of 120 participants were enrolled, allowing for a non-evaluable rate of up to 13%

Fedorak 2015 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible subjects were assigned to 1 of 2 treatment groups in a 1:1 ratio by random allocation that was based on a computer-generated randomization schedule prepared before the study by Robarts Inc" Comment: computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "The site investigator, study coordinator, and patient were blinded to the treatment allocation during double-blind treatment days 1-90" Comment: insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators and patients were unaware of the treatment assignment." And "The study drug and the placebo were identical in taste, smell, colour, texture, and consistency" Comment: double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Investigators and patients were unaware of the treatment assignment" Comment: study was also referred to as "double-blinded". Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The primary efficacy analyses were performed according to the intent-to-treat principle" Comment: proportion and reasons for attrition were balanced across groups
Selective reporting (reporting bias)	High risk	Quote: "The CDAI and IBDQ scores were similar in the 2 treatment groups (data not shown)" Comment: trial registration available (NCT00175292), however results of proposed secondary outcomes of quality of life and disease activity were only reported as being similar between groups. No further information provided for this outcome

Fedorak 2015 (*Continued*)

Other bias	Low risk	Quote: "The baseline characteristics were similar in the 2 treatment groups. No important differences were observed in age, gender, duration or characteristics of Crohn's disease, medication use immediately before surgery, number of previous surgical resections, CDAI, or IBDQ scores" Comment: groups well balanced at baseline. Study funded by VSL Pharmaceuticals Inc. Authors indicate that representatives from VSL Pharmaceuticals Inc had the opportunity to review and comment on the study design and on the manuscript, however the principal investigators made the final decisions regarding the design of the trial, and all of the authors had access to the study data and reviewed and approved the content of the manuscript. No other apparent sources of bias detected
All domain risk of bias	Unclear risk	High

Florent 1996

Methods	**Study design:** RCT, multicentre **Setting:** France and Belgium; 12 medical centres; 1989 to 1991
Participants	**Inclusion:** All patients treated by "curative" resection for CD and whose anastomosis was within the reach of colonoscopy were eligible for the study. Crohn's disease diagnosis was established by the convergence of clinical, radiological, endoscopic, and histological data **Exclusion:** Pregnant or breastfeeding women; women of childbearing potential not receiving effective contraception; having a permanent stoma; having undergone a small intestinal resection of more than 100 cm prior to the pretrial operation; and a history of peptic ulcer, a known hypersensitivity to salicylates, or a significant renal, hepatic, or haematological disorder **Age (IG1/IG2) mean (SD):** 33.5 ± 12 overall; 35 ± 13 vs 32 ± 11; overall age not reported **Sex (M:F):** 56:70 overall; (23:42) vs (33:28) **Type of surgery:** Emergency 45; elective 161 **Previous surgery (IG1 + IG2):** 1st 166; 2nd 40 **Start of intervention after surgery:** ≤ 15 days **Medication use (IG1 + IG2):** MES 153; steroids 123; antibiotics 71; immunosuppressants 20 **Smoker (IG1/IG2):** (17/65) vs (22/61) **Number randomised (n = 126):** 65/61 **Number analysed (n = 106):** (55/65) vs (51/61) **Postrandomisation exclusion (n = 14)**: (8/65) vs (6/61) (lost to follow-up 5 (5/0);

Florent 1996 (*Continued*)

	intercurrent pathology 2 (1/1); protocol violation 3 (2/1); error of inclusion 1 (0/1); colonoscopy failure/refusal 3 (0/3))
Interventions	**Group 1:** MES (Claversal), two 500 mg tablets 3 times daily **Group 2:** Placebo, two 500 mg tablets 3 times daily **All participants:** Metronidazole and antibiotics were allowed within the perioperative period. Sulfasalazine, corticosteroids (except for substitutive doses of hydrocortisone in participants with poststeroid adrenal insufficiency), and immunosuppressive agents were not allowed during the trial
Outcomes	**Duration of study:** 12 weeks 1.**Endoscopic recurrence** defined as the presence of ulcerative lesions at the anastomotic level (aphthous, superficial or deep) owing to its poor reproducibility, classified according to Rutgeerts and colleagues (i $\geq$ 1) 2. **CDAI score**
Notes	**Funding source:** Supported by a grant from SmithKline Beecham Laboratories **Conflict of interest:** Not reported **Power calculation:** An assumption was made that 80% of participants on placebo would have an endoscopic relapse. A reduction of 30% in the relapse rate in the Claversal group was considered as the minimal clinical significant decrease. The number of participants required was 50 per arm. Estimating that 20% of patients would prove to be not evaluable, a total of 126 participants were randomised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was carried out using a permutation table within each centre" Comment: participants were classified into 3 categories, and it seems stratified randomisation using permuted blocks was used. However, no further details provided
Allocation concealment (selection bias)	Unclear risk	Quote: "The treatment was started as soon as feeding was resumed, and no later than the 15th postoperative day, and was administered blindly over 12 weeks" Comment: insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The treatment was started as soon as feeding was resumed, and no later than the 15th postoperative day, and was administered blindly over 12 weeks" Comment: study is placebo controlled, but no information is provided regarding the placebo tablet or whether interventions

Florent 1996 (*Continued*)

		were sufficiently identical to ensure blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates and reasons for attrition were balanced across groups.
Selective reporting (reporting bias)	High risk	Data on CDAI reported as means ± SD. Clinical relapse CDAI ≥ 200 as one of reasons for withdrawal not reported, although it should have been as CDAI was assessed at 12 weeks
Other bias	Low risk	Groups balanced at baseline, except for ESR, which was significantly higher in the MES group. We did not consider this sufficient to introduce bias. No other apparent sources of bias detected
All domain risk of bias	Unclear risk	High

Fukushima 2018

Methods	**Study design:** RCT, multicentre **Setting:** Japan/13 centres
Participants	**Inclusion:** Patients who underwent intestinal or colonic resection, or both, with anastomosis between normal ileum and colon (ileo-colonic anastomosis) or colon and colon (colo-colonic anastomosis), with no macroscopic lesions left in the remnant intestine **Exclusion:** A history of more than 3 intestinal resections; infectious diseases, including sepsis, tuberculosis, viral hepatitis, opportunistic infections, and other chronic infections; demyelinating disease; congestive heart failure; lymph proliferative disorder; malignant tumour; and the presence of a stoma **Age (IG1/IG2) mean (range):** 36.6 (19 to 55) vs 37.6 (23 to 74); overall age not reported **Sex (M:F):** 30:13 overall; (17:4) vs (13:9) **Type of surgery:** Ileum only 1 (0/1); ileo-caecum 24 (11/13); ileo-caecum and colon 3 (2/1); colon only 10 (6/4) **Previous surgery (IG1 + IG2):** 2nd 5 (2/3); 3rd 1 (0/1) **Start of intervention after surgery:** ≤ 4 weeks **Medication use (IG1 + IG2):** Prior infliximab (4/2) **Smoker (IG1/IG2):** (5/21) vs (2/22) **Number randomised (n = 43):** 21/22 **Number analysed (n = 43):** (21/21) vs (22/22) **Postrandomisation exclusion (n = 10)**: (4/21) vs (6/22) (not meeting criteria 4 (2/2); dropout 5 (2/3); declined participation 1 (0/1))

Fukushima 2018 (*Continued*)

Interventions	**Group 1:** IFX at 5 mg/kg at 0, 2, and 6 weeks, followed by every 8 weeks for 2 years **Group 2:** No treatment **All participants:** Participants who had been receiving IFX within 8 weeks before surgery continued to receive IFX with intervals of 8 weeks. The concomitant use of immune modulators (e.g. azathioprine and 6-MP) and immune-suppressants (e.g. cyclosporine and tacrolimus) was not allowed in either group
Outcomes	**Duration of study:** 24 months 1. **Endoscopic and/or clinical recurrence** at 2 years: endoscopic recurrence defined by a score of i3 or i4 and/or clinical relapse defined as > 150 2. **Endoscopic recurrence only** defined as score of i3 or i4 3. **Clinical relapse only** defined as CDAI > 150 4. **Adverse events** 5.**Withdrawal due to adverse events**
Notes	**Funding source:** Grant from the Intractable Diseases, Health and Labor and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan **Conflict of interest:** 2 authors serve as consultants for Tanabe Mitsubishi Pharma Co., Ltd; 10 authors received lecture fees from Tanabe Mitsubishi Pharma Co., Ltd **Power calculation:** Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible and consenting patients were assigned randomly to be treated with or without infliximab (IFX) by Keio University Hospital, Clinical and Translational Research Center, within 4 weeks of resection" Comment: insufficient information to make judgement. However, authors contacted, response as follows (quote): "In practice, when patients agreed with the study, we sent a fax to the Keio University Hospital, Clinical and Translational Research Center, where randomization was carried out using random number. Then Keio University Hospital, Clinical and Translational Research Center sent back the decision (Infliximab or without infliximab). Random number generated by computer". Comment: computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Appears to have been centrally allocated based on the information above

Fukushima 2018 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label pilot study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Highly unlikely, open-label pilot study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patients who dropped out of follow-up, did not undergo endoscopy at 24 months, or had adverse effects leading to withdrawal from the study were treated as recurrent cases" Comment: ITT analysis applied, however there was about 25% attrition rate which was considered insufficient to introduce bias
Selective reporting (reporting bias)	Low risk	Trial registration available (UMIN000002604), and all proposed outcomes were reported
Other bias	Low risk	Quote: "There were no statistical differences between the two groups in history of IFX therapy, smoking behavior, surgical indication, site of disease, or type of anastomosis" Comment: groups balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	High risk	Very high

Gossum 2007

Methods	**Study design:** RCT, multicentre **Setting:** Belgium, 9 university/teaching hospitals; 2001 to 2004
Participants	**Inclusion:** Patients undergoing a first or subsequent ileocolic resection with a primary anastomosis for disease confined to the ileum and adjacent colon were eligible for enrolment. Patients with minimal evidence of Crohn's disease at other sites (aphthoid erosions or microscopic inflammatory changes) **Exclusion:** 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 **Age (IG1/IG2) mean (SD):** 37 ± 13 overall; 38.7 ± 14.5 vs 35 ± 11.7 **Sex (M:F):** 37:33 overall; (19:15) vs (18:18) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 18 (7/11)

	Start of intervention after surgery: ≤ 1 week **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** (13/34) vs (12/36) **Number randomised (n = 70):** 34/36 **Number analysed (n = 70):** (34/70) vs (36/70) **Postrandomisation exclusion (n = 21)**: (7/34) vs (14/36) (protocol violation 7 (4/3); dropouts 14 (3/11))
Interventions	**Group 1:** Probiotic *Lactobacillus johnsonii* (LA1, Nestec) in freeze-dried form and blended with maltodextrin at 1010 CFU/day. The LA1 powder was supplied in foil sachets (weight 2 g) containing 1010 CFU of probiotics **Group 2:** The placebo was maltodextrin only as a powder of the same appearance and weight, also in individual foil packets **All participants:** Both probiotics and placebo were administered in combination with an enteral formula at 120 mL/day (ACD004, Nunspeet, Netherlands; Konolfingen, Switzerland). No other medication (including antidiarrhoeal agents) was allowed during the study period. No other fermented products or yoghurts were allowed during the 12 weeks of treatment. Participants were enrolled prior to elective ileo-caecal resection. All participants enrolled in the study received 3 days of antibiotics (amoxicillin/clavulanic acid 500 mg orally 3 times a day) prior to surgery (intestinal decontamination)
Outcomes	**Duration of study:** 12 weeks 1. **Endoscopic recurrence** defined as i ≥ 1 according to the Rutgeerts scoring system: i1 to i2 mild to moderate; i3 to i4 severe. Relapse defined as i ≥ 1 2. **Clinical recurrence** defined as CDAI > 150 points or an increase in CDAI score of > 70 points or higher from baseline 3.**Histological score** assessed by the Geboes scoring system 4.**Adverse events** 5.**Severe adverse events** 6. **Withdrawal due to adverse events**
Notes	**Funding source:** Study was supported by a research grant from Nestlé Research Center, Vers-chez-les-blanc, Lausanne, Switzerland **Conflict of interest:** Not reported **Power calculation**: Detection of a difference of 1 endoscopic score (5 scores: i0 to i4) between the 2 groups at 0.05 and 80% requires a sample size of 31 participants per group (Pass 6.0 program). To compensate for potential missing data, 20% additional participants were recruited (37 participants per group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization between the two groups was centralized and performed on current smoking status at the time of surgery as balancing the factor using the Nestle Trial Balance program" Comment: centralised random sequence

Gossum 2007 (*Continued*)

		generation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The identity of the treatment sachet was blind to patients, support staff, and investigators (numerical codes). Treatment codes were broken only by the statistician after completion of the trial" Comment: double-blinded, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Biopsy samples of the neoterminal ileum were taken and assessed blindly by two pathologists" Comment: outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All data were analysed according to both an intention to treat (ITT) and a per-protocol (PP) approach" Comment: ITT analysis applied; all participants accounted for
Selective reporting (reporting bias)	Low risk	Protocol not available. All outcomes stated in the methods section including adverse events were reported
Other bias	Low risk	Groups well balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Hanauer 2004

Methods	**Study design:** RCT, multicentre **Setting:** USA and Belgium/5 centres; 1992 to 1996
Participants	**Inclusion:** Between 18 and 65 years of age, with diagnosis of CD for at least 6 months and scheduled for curative ileo-caecal resection; ability to start oral nutrition within 7 days of operation, need for curative ileo-caecal resection, and resection margins free of inflammation **Exclusion:** Active perianal disease or any active disease in other segments of the intestine, anti-TNF and/or investigational treatment within 4 months prior to surgery; current treatment with 5-ASA, azathioprine/6-MP, or methotrexate; bowel surgery performed less than 3 months previously; history of colostomy or ileostomy; infections, neoplasia, or uncontrolled diseases; or anticipation of non-compliance with protocols. Patients who were receiving steroids preoperatively were tapered and weaned according to a strict schedule

	Age (IG1/IG2) mean (SD): 34.4 ± 11.0 overall; 34.9 ± 11.5 vs 34.1 ± 10.9 vs 34.2 ± 10.9 **Sex (M:F):** 60:71 overall; (23:24) vs (19:25) vs (18:22) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 18 (7/11) **Start of intervention after surgery:** Therapy initiated before postoperative hospital discharge **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 131):** 47/44/40 **Number analysed (n = 131):** (47/131) vs (44/131) vs (40/131) **Postrandomisation exclusion (n = 27)**: (12/47) vs (7/44) vs (8/40) (withdrew consent 5 (1/2/2); surgical complication 3 (2/0/1); non-compliance 9 (2/4/3); lost to follow-up 10 (4/2/4))
Interventions	**Group 1:** 50 mg of 6-MP (Purinethol) once daily **Group 2:** 3 g of MES (Pentasa); 4 capsules of 250 mg, 3 times daily **Group 3**: Identical matching placebo **All participants:** Presurgical therapy, including aminosalicylates, antibiotics, or immunomodulators, was discontinued before surgical resection and was not allowed during the postoperative trial. Preoperative treatment with corticosteroids was completely tapered by 3 months after hospital discharge at a rate determined by the treating physician. No concurrent treatment for Crohn's disease, aside from topical therapy for perianal disease, was allowed during the duration of the trial. Continuous use of non-steroidal anti-inflammatory drugs was not allowed during the study. If the WBC and platelet counts fell below 4500/L or 150,000/L, respectively, the dosage of 6-MP was reduced by one-half
Outcomes	**Duration of study:** 24 months 1.**Endoscopic recurrence** defined as i ≥ 1 according to the Rutgeerts scoring system: i1 to i2 mild to moderate; i3 to i4 severe. Relapse defined as i ≥ 1 2.**Clinical recurrence** defined as CDAI > 150 points or an increase in CDAI score of > 70 points or higher from baseline. (ITT data derived from number randomised minus number in clinical remission at the end of the study.) 3. **Histological score** assessed by the Geboes scoring system 4.**Adverse events** 5.**Serious adverse events** 6.**Withdrawal due to adverse events**
Notes	**Funding source:** Not reported, however email received from authors on 2 August 2018 stated that study was funded by Crohn's and Colitis Foundation **Conflict of interest:** Not reported, however email received from authors on 2 August 2018 declared none **Power calculation**: Sample size calculations were performed for the endoscopic criteria, using 2-sided of 0.05 and 80% power, based on a predicted endoscopic recurrence of 75% at 1 year in the placebo group. A sample size of 50 in each group allows sufficient power to detect a 40% reduction in mild Crohn's disease lesions and a 75% reduction in more severe lesions at 1 year

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quotes: "Patients were randomized by a central computer by permuted blocks of 6 (unknown to investigators) per center to receive mesalamine (Pentasa; Marion Merrill Dow, Kansas City, MO) 3 g daily, 6-MP (Purinethol; Burroughs Wellcome, Research Triangle Park, NC) 50 mg daily, or placebo" Comment: computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Quotes: "Medications were prepared and dispensed by an assigned pharmacist at each site's investigational pharmacy who was not directly involved in the care of the patients" Comment: treatment controlled by pharmacies at each centre
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quotes: "Medications were prepared and dispensed by an assigned pharmacist at each site's investigational pharmacy who was not directly involved in the care of the patients" and "An evaluating (treating) physician followed up each patient and was blinded as to the study drug and laboratory results" Comment: placebo-controlled, double-blind RCT. However, it is unclear whether both study drugs were sufficiently identical to the placebo to blind study participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "Patient evaluation consisted of assessments of clinical, endoscopic, and radiographic disease activity at each study site by the blinded physician" and "Colonoscopic examinations with endoscopic descriptions and photography of the anastomosis and preanastomotic ileum were performed by the blinded investigators (all gastroenterologists) at months 6, 12, and 24" and "Radiographic interpretations were performed by the blinded inflammatory bowel disease radiologist at each institution" Comment: assessors blinded to treatment

Hanauer 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "The clinical recurrence rates were determined using ITT" Comment: ITT analysis applied, attrition was similar, low, and balanced across groups
Selective reporting (reporting bias)	Low risk	Comment: all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "There were no statistical differences in patient age, sex, disease duration, indications for surgical resection, or preoperative disease activity among the 3 groups" Comment: groups well balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Hellers 1999

Methods	**Study design:** RCT, multicentre **Setting:** Belgium, Denmark, France, Germany, Italy, the Netherlands, the UK, and Sweden/13 centres; 1992 to 1993
Participants	**Inclusion:** Patients who were scheduled for resectional surgery for ileocolonic CD who had given their informed consent at the screening visit were eligible for the study **Exclusion:** 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 **Age (IG1/IG2) mean (range):** overall not reported; 34 (20 to 76) vs 36 (17 to 81) **Sex (M:F):** 62:67 overall; (35:28) vs (27:39) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 36 (19/17) **Start of intervention after surgery:** < 2 weeks **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 131):** 63/67 **Number analysed (n = 129):** (63/63) vs (66/67) **Postrandomisation exclusion (n = 8)**: (4/63) vs (4/67) (lost to follow-up 1 (1/0); other reasons 6 (3/3); did not start treatment 1 (0/1))
Interventions	**Group 1:** 6 mg/day budesonide as single daily morning doses for 52 weeks **Group 2:** Placebo as single daily morning doses for 52 weeks **All participants:** Follow-up visits were carried out after 4 weeks (63 days) and after 13, 26, 39, and 52 weeks of treatment (61 weeks). Use of systemic glucocorticoids had to be discontinued within 30 days of surgery. No other concurrent medication for the treatment of CD, such as sulfasalazine, olsalazine, MES, 4-aminosalicylic acid, metronidazole, immunosuppressive agents, or tuberculostatic agents, was permitted during the

	study. Antibiotics were allowed in the immediate postoperative period but had to be discontinued before the study treatment was started. Antidiarrhoeals such as loperamide and other opiates were allowed
Outcomes	**Duration of study:** 52 weeks 1. **Endoscopic recurrence** defined as i ≥ 2 according to the Rutgeerts scoring system: i1 to i2 mild to moderate; i3 to i4 severe. Relapse defined as i ≥ 1 2. **Clinical recurrence** defined as CDAI > 200 3.**Adverse events** 4.**Serious adverse events** 5.**Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: With 50 participants per group, there was an 80% probability of a significant difference in endoscopic recurrence rate if the budesonide recurrence rate was 40%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were then randomized to treatment with either budesonide CIR, 6 mg/day[...] The randomization code was not broken until each patient's file was complete and approved for statistical analysis and adverse event evaluation" Comment: it is unclear how the randomisation codes were generated
Allocation concealment (selection bias)	Unclear risk	Insufficient data to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The randomization code was not broken until each patient's file was complete and approved for statistical analysis and adverse event evaluation" Comment: study is placebo controlled, and blinding appeared to have remained unbroken until all outcomes were collected
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The randomization code was not broken until each patient's file was complete and approved for statistical analysis and adverse event evaluation" Comment: not explicitly stated, however blinding appeared to have remained unbroken until all outcomes were collected

Hellers 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates and reasons were similar and balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "The two groups were similar in terms of characteristics and disease history" Comment: baseline characteristics were balanced across groups, and there were no other apparent biases
All domain risk of bias	Low risk	Low/unclear

Herfarth 2006

Methods	**Study design:** RCT, multicentre **Setting:** Not stated (multicentre RCT)
Participants	**Inclusion:** People with Crohn's who had undergone resective surgery **Exclusion:** Homozygous thiopurine methyltransferase (*TPMT*) **Age:** Not reported **Sex:** Not reported **Type of surgery:** Not reported **Previous surgery:** Not reported **Start of intervention after surgery:** within 2 weeks postoperative **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 79):** 42/37 **Number analysed (n = 37):** 18/19 **Postrandomisation exclusion (n = 42)**
Interventions	**Group 1:** 2.0 to 2.5 mg/g body weight/day azathioprine **Group 2:** 4 g 5-ASA/day **All participants:** Not stated
Outcomes	**Duration of study:** 1 year (study was discontinued after 1 year) 1.**Treatment failure** (due to severe endoscopic recurrence, lack of efficacy, and adverse events related to study drug) 2.**Clinical or severe endoscopic relapse** 3.**Severe endoscopic relapse** 4. **Clinical relapse** (review author calculation: clinical or severe endoscopic relapse minus severe endoscopic relapse) 5. **Adverse events** 6. **Withdrawal due to adverse events**

Notes	**Funding source:** Dr. Falk Pharma GmbH, Freiburg, Germany **Conflict of interest:** Not reported **Power calculation:** Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients in the present study were assigned to one of the two treatment groups (5-ASA or azathioprine) at random For creation of the randomisation list the programme 'Rancode +' (version 3.6) of IDV, Gauting (Germany) was used. The randomisation into two treatment groups was performed in blocks of four. After voluntary written informed consent was obtained and basic selection criteria were checked, the investigator requested the allocation of a unique patient code number (randomisation number, consecutively allocated to each patient), and received medication packs with the randomisation number for the patient" Comment: confirmed by correspondence from Muller R (2 May 2012)
Allocation concealment (selection bias)	Low risk	"The randomization code was prepared and stored by a statistician from a CRO, who was not involved in the conduct nor in the analysis of the study. The Qualified Person of the Sponsor and the contract manufacturer responsible for the preparation of the double-dummy patients sets received a copy of the randomization list, which was safely stored at both sites, without allowing access by other people. Neither the investigator nor the study team from the clinical operation from the sponsor nor the CRO had access to the random list" Comment: confirmed by correspondence from Muller R (2 May 2012)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"This was a double-blind, double-dummy study. Patients randomized to administer 5-ASA had to take 5-ASA VERUM tablets AND azathioprine PLACEBO tablets. Patients randomized to receive azathioprine

		had to administer azathioprine VERUM tablets AND 5-ASA PLACEBO tablets Therefore, neither the investigator, nor the patients, nor the sponsor were ware of the TX a patient received until the database was clean, closed, and the code was broken" Comment: confirmed by correspondence from Muller R (2 May 2012)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"This was a double-blind, double-dummy study. Patients randomized to administer 5-ASA had to take 5-ASA VERUM tablets AND azathioprine PLACEBO tablets. Patients randomized to receive azathioprine had to administer azathioprine VERUM tablets AND 5-ASA PLACEBO tablets Therefore, neither the investigator, nor the patients, nor the sponsor were ware of the TX a patient received until the database was clean, closed, and the code was broken" Comment: confirmed by correspondence from Muller R (2 May 2012)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The study was stopped prematurely after an interim-analysis due to a high therapy failure rate. 38 patients (AZA 18 pat.; 5-ASA 20 pat.) completed the study and could be evaluated regarding the primary endpoint therapy failure. The other pat. terminated the trial prematurely due to the study stop, but were also evaluated for adverse events (AE) and adverse drug reactions (ADR)" Comment: 51% of randomised participants discontinued. High risk for primary outcome and low risk for adverse events and withdrawal due to adverse events
Selective reporting (reporting bias)	Unclear risk	Insufficient information as trial registration was not available and study was published as abstract
Other bias	Unclear risk	Insufficient information as study was published as abstract
All domain risk of bias	Low risk	Low/unclear

Herfarth 2013

Methods	**Study design:** RCT, multicentre **Setting:** USA, 6 centres; 2008 to 2011
Participants	**Inclusion:** Patients who had undergone ileal or ileocolonic resection with ileocolonic anastomosis for CD within the previous 2 weeks **Exclusion:** Gross evidence of CD at the operative margins or in the proximal or distal segments of the intestine. Other exclusion criteria were the presence of a stoma, serum creatinine concentration > 1.5 mg/dL, the desire to become pregnant during the study, known malignancies, intolerance to quinolones, or previous long-term therapy with ciprofloxacin of > 4 weeks prior to surgery **Age (IG1/IG2) median (range):** overall not reported; 33 (19 to 70) vs 27 (18 to 61) **Sex (M:F):** 18:15 overall; (10:7) vs (8:8) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 18 (7/11) **Start of intervention after surgery:** ≤ 2 weeks **Medication use (IG1 + IG2):** MES 9 (4/5); immunosuppression 8 (3/5); steroids 11 (7/4) **Smoker (IG1/IG2):** (4/17) vs (0/16) **Number randomised (n = 33):** 17/16 **Number analysed (n = 33):** (17/17) vs (16/16) **Postrandomisation exclusion (n = 11)**: (6/17) vs (5/16) (need for prohibited medication 2 (1/1); non-compliance 5 (3/2); lost to follow-up 3 (2/1); consent withdrawals 1 (0/1))
Interventions	**Group 1:** Oral treatment with ciprofloxacin 500 mg twice daily for 6 months **Group 2:** Oral treatment with identical-appearing placebo twice daily for 6 months **All participants:** No other treatments for CD or therapies involving more than 10 days of broad-spectrum antibiotics were permitted. Examinations were performed at weeks 4, 12, and 24 after the start of medication and additionally by phone at weeks 8, 18, and 28
Outcomes	**Duration of study:** 6 months 1. **Endoscopic recurrence** defined as i ≥ 2 according to the Rutgeerts score or a Marteau score ≥ c2 2. **Clinical recurrence (Harvey Bradshaw index ≥ 5)** 2. **Adverse events** 3. **Withdrawal due to adverse events**
Notes	**Funding source:** Senior Research Award of the Crohn's and Colitis Foundation of America and the National Institute of Diabetes and Digestive and Kidney Diseases **Conflict of interest:** Not reported **Power calculation**: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized in a 1:1 ratio to oral treatment with ciprofloxa-

		cin 500 mg or identical appearing placebo twice daily for 6 months. Randomization took place at the trial central pharmacy at the University of North Carolina. Randomization was performed by permuted block randomization with a block size of 4 per site" Comment: block random sequence generation
Allocation concealment (selection bias)	Low risk	Centralised allocation by the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo- controlled, double-blind trial, however no information regarding the blinding of personnel provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Also photo-documentation of the anastomosis and neoterminal ileum of each patient was reviewed in a blinded fashion by two of the investigators (H.H., K.I.). All scores of this second evaluation were in agreement with the initial evaluation" Comment: outcome assessors blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "For the ITT analysis patients without ileocolonoscopy and clinical evaluation at the 6-months visit were considered to have endoscopic and clinical recurrence of CD" Comment: ITT analysis applied; however, overall attrition rate of over 30% when compared to event risk of 24% raises concerns about bias
Selective reporting (reporting bias)	Low risk	Trial registration is available (NCT00609973). All proposed outcomes were reported
Other bias	Low risk	Baseline characteristics balanced. No other apparent sources of bias detected
All domain risk of bias	Unclear risk	High risk

Lochs 2000

Methods	**Study design:** RCT, multicentre **Setting:** Austria, Denmark, Germany, Norway, Sweden, and Switzerland; 29 university/teaching hospitals; 1992 to 1996
Participants	**Inclusion:** Adults (18 to 70 years) who underwent a resective surgical procedure (radical or non-radical) for a CD-specific lesion at 1 of the participating centres; diagnosis of CD established by generally accepted endoscopic, histological, 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:** Exclusion criteria included contraindications for use of MES; 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 **Age (IG1/IG2) mean (SD):** 33.6 ± 10.1 overall; 33.5 ± 10.0 vs 33.8 ± 10.2 **Sex (M:F):** 156:162 overall; (71:81) vs (85:81) **Type of surgery:** radical 244 (121/123); non-radical 75 (35/40) **Previous surgery (IG1 + IG2):** 18 (7/11) **Start of intervention after surgery:** ≤ 10 days **Medication use (IG1 + IG2):** Sulfasalazine 190 (96/94); metronidazole 32 (10/22); immunosuppressants 18 (8/10); corticosteroids 187 (86/101); TPN 35 (16/19) **Smoker (IG1/IG2):** not reported **Number randomised (n = 324):** 154/170 **Number analysed (n = 318):** (152/154) vs (166/170) **Postrandomisation exclusion (n = 20)**: (7/34) vs (13/36) (lost to follow-up 14 (5/9); did not start treatment 6 (2/4))
Interventions	**Group 1:** 4 g MES (Pentasa) per day divided into 3 doses (1.5, 1, and 1.5 g). 1 tablet of Pentasa contains 500 mg encapsulated in ethylcellulose microgranules and pressed to form a tablet with microcrystalline cellulose **Group 2:** Placebo tablets of identical appearance and consistency containing additional microcrystalline cellulose to compensate for the MES microgranules **All participants:** Corticosteroids were permitted to be tapered by standardised stepwise dose reductions within 6 weeks. Concomitant medication such as glucocorticoids with the exception of initial tapering, non-steroidal anti-inflammatory drugs, immunosuppressive drugs, metronidazole, methotrexate, sulfasalazine, and other 5-aminosalicylates were not allowed. Symptomatic treatment with antidiarrhoeal, antacid, or spasmolytic medication was allowed but had to be thoroughly documented for calculation of the CDAI. Similarly, participants were requested to report precisely any other concomitant medication in their diary. Participants were supplied with study medication for the subsequent 3 months at each follow-up visit. Any tablets not used had to be returned. MES and acetylmesalazine were determined in blood samples drawn at each visit. Participants were considered non-compliant if medication was interrupted for a total of > 10% of their individual trial course. Endoscopic evaluation of the colon and, if possible, of the anastomosis was recommended at 6 weeks and 18 months after surgery or at the time of clinical relapse

Outcomes	**Duration of study:** 18 months **1. Endoscopic recurrence** defined as i ≥ 1 according to Rutgeerts and colleagues **2. Clinical recurrence** 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, indication for surgery; development of a new fistula; and occurrence of a septic complication. (ITT data estimated as: number randomised − number in remission at 18 months.) **3. Adverse events** **4. Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: Based on a maximum relapse rate with placebo of 50% and an absolute effect size of 15% with the active drug, a sample size of 150 participants per treatment group was calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization scheme was provided by the Institut für Medizinische Dokumentation und Statistik at the University of Köln at the beginning of the trial and forwarded to the Department of Galenics at Ferring A/S, Denmark. Randomization was performed in blocks of 10 for each of the participating centers" Comment: computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "In addition, each center retained sealed opaque envelopes containing patient numbers and treatment allocations, which were only allowed to be opened in case of a serious adverse event that necessitated disclosure of the type of treatment" Comment: unclear whether envelops were sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo tablets of identical appearance and consistency contained additional microcrystalline cellulose to compensate for the mesalamine microgranules.. . All patients and investigators were blinded regarding treatment allocation" Comment: placebo blinded

Lochs 2000 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization was performed in blocks of 10 for each of the participating centers. This information was kept confidential at the Department of Quality Assessment at Ferring and the statistical center in Cologne and was only available to the Department of Galenics [...] An Endpoint Committee consisting of 2 physicians and 1 surgeon, not participating in the trial, made a final decision about questionable cases of protocol violations and relapses" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "Outcome measures were analysed in all randomized patients who had taken at least 1 dose of study medication (intention-to-treat population)" Comment: attrition rates and reasons were balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "No significant differences were detected between the 2 treatment groups for any of the parameters investigated" Comment: groups well balanced at baseline. No additional sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Lopez Sanroman 2017

Methods	**Study design:** RCT, multicentre **Setting:** Spain, 22 centres; 2012 to 2015
Participants	**Inclusion:** Adults (18 to 70 years) who underwent a resective surgical procedure (radical or non-radical) for a CD-specific lesion at 1 of the participating centres; diagnosis of CD established by generally accepted endoscopic, histological, 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:** Contraindications for use of MES; 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 **Age (IG1/IG2) median (interquartile range)**: overall age not reported; 37.00 (31.00 to 47.00) vs 35.00 (30.0 to 40.0) **Sex (M:F):** 42:42 overall; (23:16) vs (19:26) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 6 (3/3) **Start of intervention after surgery:** After surgery (consent obtained before surgery) **Medication use (IG1 + IG2):** Glucocorticoids 80 (38/42); immunosuppressants (thiopurines or methotrexate) 63 (28/35); anti-TNFα 49 (21/28) **Smoker (IG1/IG2):** 20 (9/11) **Number randomised (n = 85):** 40/45 **Number analysed (n = 84):** (39/40) vs (40/40) **Postrandomisation exclusion (n = 3)**: (1/40) vs (2/45) (consent withdrawal before treatment 1 (0/1); loss to follow-up 2 (1/1))
Interventions	**Group 1:** AZA 2.5 mg/kg/day for 1 year. Metronidazole 250 mg 3 times a day by mouth was added for the first 3 months **Group 2:** ADA 160 mg subcutaneously, then 80 mg at Week 2, or 40 mg at Week 4 and every 2 weeks thereafter for 1 year. Metronidazole 250 mg 3 times a day by mouth was added for the first 3 months **All participants:** Adherence to therapy was assessed by direct questioning and by counting of returned medication
Outcomes	**Duration of study:** 52 weeks **1. Endoscopic recurrence** defined as i $\geq$ 2b, 3 and 4 based on Rutgeerts score (24 and 52 weeks) **2. Clinical recurrence** defined by 1 of the following: increase in CDAI above 200 (24 and 52 weeks) (CDAI $\geq$ 200: ITT data derived from number randomised − remissions) **3. Radiologic recurrence rate** **4. Health-related quality of life** **5. Adverse events** **6. Serious adverse events** **7. Withdrawal due to adverse events**
Notes	**Funding source:** Unrestricted grant from AbbVie (Spanish Working Group on Crohn's Disease and Ulcerative Colitis). The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decisions concerning publication. The authors had unrestricted access to the data; the decision to submit the paper for publication was solely and entirely to theirs **Conflict of interest:** All authors have declared conflict of interest (mainly grants, personal fees, collaboration with AbbVie outside the submitted work, research funding from AbbVie, etc.) **Sample size:** The difference in the proportion of endoscopic recurrence between treatment groups was estimated at 35% (10% for ADA + metronidazole and 45% for AZA + metronidazole), considering a type I error of 5%, a 2-tailed contrast with Yates' continuity correction, 90% power (1-type II error), and an allocation ratio of 1:1. 38 participants per treatment group would therefore be needed. Withdrawals were estimated at 10%. The minimal sample was estimated at 84 evaluable participants

Lopez Sanroman 2017 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Central randomisation was based on a pregenerated block randomisation list stratified by centre." and "Patients were assigned [1:1] to..." Comment: central randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation was concealed by means of a computer-generated randomisation schedule without stratification or block allocation" Comment: insufficient description
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Neither patients nor investigators were blinded to the administered treatment" Comment: no blinding of personnel and participants performed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A video recording of the last 15 cm of the neo-terminal ileum was evaluated by an endoscopist blinded to treatment allocation and experienced in application of the Rutgeerts score [VP]" and "...MRE, which was evaluated centrally by an experienced blinded reader [JR]" Comment: outcome assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We defined the following populations: 1] the intention-to-treat [ITT] population, which included all consenting patients who were randomised and received at least one dose of the study medications" Comment: ITT analysis applied, reasons for withdrawal reported, and attrition rates were balanced across groups
Selective reporting (reporting bias)	High risk	Trial registration was available (NCT01564823), and all prespecified outcomes were reported in the study except for health-related quality of life, which was only reported as a P value in an abstract

Other bias	Low risk	Quote: "The groups were similar regarding baseline characteristics, including smoking status, previous resections, CD phenotype, previous perianal disease, and previous drug exposure" Comment: groups well balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	High risk	Very high

Marteau 2006

Methods	**Study design:** RCT, multicentre (The GETAID study) **Setting:** France, Belgium, Switzerland, and the Netherlands; 2002 to 2004
Participants	**Inclusion:** Male and female patients at least 18 years of age were eligible to participate if they had: (a) undergone recent surgical resection for ileal, ileocolonic, or colonic CD, removing all macroscopic lesions, with an anastomosis that could be reached by ileocolonoscopy; (b) cumulative small bowel resection(s) of less than 1 m; and (c) no other intestinal resection during the previous 5 years **Exclusion:** Patients receiving antibiotics for more than 2 weeks and those treated with aminosalicylates or immunosuppressants for more than 3 weeks after surgery were not eligible, neither were those with any other disease or condition that might interfere with the study assessments (as judged by the investigator). Patients who had participated in another clinical study in the previous 30 days; women of childbearing potential who were not using effective contraception; pregnant or lactating women; and patients who had undergone total or subtotal colectomy, intestinal bypass or stricturoplasty, stomy, carcinoma resection, or abscess drainage were also ineligible **Age (IG1/IG2) median (interquartile range):** Not stated overall; 32 (27 to 42) vs 29 (27 to 34) **Sex (M:F):** 55:43 overall; (26:22) vs (29:21) **Type of surgery:** Ileal 7 (6/1); ileocolonic 89 (40/49); colonic (segmental) 2 (2/0) **Previous surgery (IG1 + IG2):** 16 (7/9) **Start of intervention after surgery:** ≤ 21 days **Medication use (IG1 + IG2):** Steroid treatment 61 (19/42) **Smoker (IG1/IG2):** Not reported **Number randomised (n = 98):** 48/50 **Number analysed (n = 98):** (48/48) vs (50/50) **Postrandomisation exclusion (n = 8)**: (5/48) vs (3/50) (lost to follow-up 6 (4/2); not evaluated 2 (1/1))
Interventions	**Group 1:** 2 packets per day of lyophilised LA1 (26109 CFU per packet) for 6 months **Group 2:** 2 packets per day of placebo (maltodextrin) for 6 months **All participants:** The packets had to be dissolved in half a glass of water just before consumption. Corticosteroids were allowed if used before surgery but had to be withdrawn gradually within 6 weeks after surgery. Concomitant medication with the following drugs was not allowed: antibiotics for more than 15 days; aminosalicylates; glucocorticoids

	(after gradual withdrawal); non-steroidal anti-inflammatory drugs; immunosuppressive drugs; anti-TNF agents; thalidomide; and other probiotics. Loperamide and colestyramine were allowed. Study visits were planned at inclusion and 3 and 6 months after surgery, and if clinical signs of recurrence occurred. Ileocolonoscopy was performed at 6 months and in case of clinical recurrence
Outcomes	**Duration of study:** 6 months 1. **Endoscopic recurrence** defined grade >1 macroscopic lesions in the ileum or colon, using Rutgeerts' classification for ileal lesions 2. **Clinical recurrence** defined as CDAI of 200 or more 3. **Severe endoscopic recurrence** defined as endoscopic score (maximum of the ileum and colon grades) of >2 3. **Adverse events**
Notes	**Funding source:** Funded by grant support from the Nestlé Research Center, Vevey, Switzerland. Study products were provided by Nestlé. All data analysis and manuscript writing was performed independently by the GETAID Study Group, with no involvement of Nestlé representatives **Conflict of interest:** All authors declared conflict of interest (supplementary material online) **Power calculation**: The hypothesis for the sample size calculation was an endoscopic recurrence rate of 50% at 6 months in the placebo group. In order to detect a 30% reduction in the endoscopic recurrence rate in the LA1 treatment arm, it was calculated that 48 participants per group had to be enrolled to guarantee a power of 80% in a 2-sided test with a type I error of 5%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "... randomisation was performed by this centre within each stratum per centre, using permutation tables of size 2 or 4, according to expected enrolment within each centre, each centre being blinded to the size of its blocks" Comment: block randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Treatment number was the first free number with the corresponding treatment in a randomised list with treatment numbers and their corresponding treatment prepared by the biostatistics centre before trial initiation" and "The same information and allocated treatment were sent to the service in charge of drug delivery, allowing the service to check that treatment was in agreement with the predefined list. Treatment was sent by this service to the

Marteau 2006 (*Continued*)

		pharmacy of the centre with protocol identification and the patient's dentification" Comment: central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blinded and "unblinding, if necessary, was made by a request to the biostatistics centre with a specific form" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The primary efficacy analysis was based on the ITT population, which included all patients in whom the primary endpoint was assessable" Comment: attrition rates and reasons were balanced across groups
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.
Other bias	Low risk	Quote: "The two treatment groups were well matched, except for a higher proportion of patients who underwent ileal and colonic resection in the placebo group, and a higher median CRP level in the LA1 group" Comment: groups well balanced at baseline; no other apparent sources of bias
All domain risk of bias	Low risk	Low/unclear

Mañosa 2013

Methods	**Study design:** RCT, multicentre **Setting:** Spain; 2004 to 2010
Participants	**Inclusion:** All consecutive adult patients with CD undergoing ileal or ileocolic resection with ileocolic or ileorectal anastomosis between January 2004 and January 2010 were invited to participate in the trial **Exclusion:** Exclusion criteria included the following: intolerance or known allergy to the study drugs; erythrocyte thiopurine methyltransferase activity < 5 U/mL red blood cells; previous treatment with thiopurines for the same indication (prevention of postoperative recurrence); antecedents of malignancy; ongoing infectious disease; pregnancy or a desire to become pregnant; intolerance to oral intake; and use of any investigational drug in the preceding 6 months

	Age (IG1/IG2) mean (SD): 35.36 ± 10.13 overall; 36.2 ± 12 vs 34.52 ± 8 **Sex (M:F):** 27:23 overall; (12:13) vs (15:10) **Type of surgery:** radical 244 (121/123); non-radical 75 (35/40) **Previous surgery (IG1 + IG2):** 18 (7/11) **Start of intervention after surgery:** Not reported **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** 23 (10/13) **Number randomised (n = 50):** 25/25 **Number analysed (n = 50):** (25/25) vs (25/25) **Postrandomisation exclusion (n = 0)**
Interventions	**Group 1:** Oral metronidazole 3 times a day for a total dose of 15 to 20 mg/kg per day for the first 3 months after the surgical procedure (AZA + MDZ) **Group 2:** The same number of placebo pills during the first 3 months after the surgical procedure. (Placebo was prepared and packaged in the Pharmacy Department of the Hospital Universitari Germans Trias i Pujol) (AZA + PLAC) **All participants:** After signing the informed consent document, all participants were treated with azathioprine (2 to 2.5 mg/kg per day) until the end of the study. Any concomitant treatment for CD (methotrexate, aminosalicylates, corticosteroids, budesonide, metronidazole (except for the first 3 months in participants randomised to metronidazole), ciprofloxacin, or anti-TNF agents) was not allowed during the study
Outcomes	**Duration of study:** 12 months 1. **Clinical recurrence** defined as a Harvey-Bradshaw index of > 7 points, together with morphological disease recurrence as documented by the endoscopic or radiological findings 2. **Severe endoscopic relapse** defined as a Rutgeerts endoscopic score of i ≥ 3 3. **Adverse events** 4. **Withdrawal due to adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: It was not possible to perform a reliable estimation of the sample size. As a consequence the trial was conceived as a pilot study with 25 participants per therapeutic arm Note: The intervention of interest was given only for the first 3 months, and outcome results were not presented for that time point. Azathioprine was given to all participants until month 12, and outcome data were reported at that time point, albeit not useful for the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed on a 1:1 basis, using a computer-generated random allocation sequence of permuted blocks of 4 patients each. The randomization process was centralized but stratified

		per participating center" Comment: stratified block randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "Azathioprine was ordinarily prescribed, whereas the study medication (metronidazole or placebo) was dispensed by the pharmacy of each participating hospital" Comment: the randomisation process was centralised, and the pharmacy of each participating hospital dispensed the study intervention. Details of central allocation were not clear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial was reportedly double blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals for reasons other than adverse events
Selective reporting (reporting bias)	Low risk	The authors indicate that the trial was registered (Eudr CT 2004-001795-39). However, we were unable to locate the trial registration. All outcomes stated in the methods section were reported
Other bias	Low risk	Groups well balanced at baseline in all parameters assessed, except for the previous use of thioprines, which was more frequent in the metronidazole group. The review author team did not consider this to be a source of bias
All domain risk of bias	Low risk	Low/unclear

McLeod 1995

Methods	**Study design:** RCT, multicentre **Setting:** Canada; 1986 to 1993
Participants	**Inclusion:** All patients who had undergone a surgical resection for Crohn's disease at 1 of the participating hospitals and who had no gross residual disease were eligible for entry provided they were randomised within 8 weeks of the date of surgery **Exclusion:** Patients with residual Crohn's disease (including gastroduodenal Crohn's

	disease) with the exception of asymptomatic anal skin tags or anal stenosis; abnormal renal function with a serum creatinine level > 130 µmol/dL or 1.5 mg/dL; if they were taking prednisone, sulfasalazine, metronidazole, or azathioprine (Imuran) and these drugs could not be discontinued **Age (IG1/IG2) mean (SD):** 38.0 ± 13.1 overall; 38.9 ± 13.1 vs 38.9 ± 13.2 **Sex (M:F):** 98:65 overall; (49:38) vs (49:27) **Type of surgery:** Small bowel resection 15 (8/7); terminal ileal/ileocolic resection 109 (59/50); segmental colon resection 7 (7/0); total abdominal colectomy 3 (1/2); proctocolectomy 25 (13/12); proctectomy 10 (3/7) **Previous surgery (IG1 + IG2):** 179 surgical resections performed in the 163 participants **Start of intervention after surgery:** ≤ 8 weeks **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 169):** 88/81 **Number analysed (n = 163):** (87/88) vs (76/81) **Postrandomisation exclusion (n = 21)**: (8/88) vs (13/81) (randomised but did not give consent 6 (1/5); refused follow-up because of personal reason 11; death due to multiple myeloma 1; moved to Europe 1; bowel resection (suspected Crohn's disease, but resected specimen was pathologically normal) 2 (reasons not reported separately))
Interventions	**Group 1:** 3 g/day of MES taken as six 250 mg tablets twice daily **Group 2:** 6 identical-looking placebo tablets twice daily **All participants:** Study medication was mailed to the participant every 3 months. At 3-month intervals, all participants were interviewed by telephone by a research nurse to determine their clinical status; ensure they were not taking any other prescribed medications; and assess their compliance. At yearly intervals, all participants were assessed by an investigator and appropriate radiological or endoscopic investigations performed. If endoscopy could not be performed, then an air contrast barium enema or ileostomy injection was performed. Once participants were judged to have symptoms caused by Crohn's disease that required treatment and there was radiographic or endoscopic confirmation of disease, they were considered a failure. Further treatment was at the discretion of their attending physician or surgeon. Compliance was determined by questioning the participants and by pill counts of all medication returned at the annual visit
Outcomes	**Duration of study:** Follow-up period 72 months maximum 1. **Symptomatic recurrence** defined as symptoms compatible with Crohn's disease that were severe enough to warrant treatment in the opinion of the investigator plus radiological or endoscopic evidence of disease using the outlined criteria (at least 1 of the following features had to be present to make the diagnosis of recurrent disease: aphthous ulcers; longitudinal or punched-out ulcers; cobblestoning or nodularity of the bowel; stricture of the bowel associated with oedema, ulceration, or erythema of the mucosa; pseudopolyps; or mucosal bridging) 2. **Endoscopic and radiologic relapse rate** defined as the presence of endoscopic or radiological evidence of disease and included both asymptomatic and symptomatic participants. At least 1 of the following features had to be present to make the diagnosis of recurrent disease: aphthous ulcers; longitudinal or punched-out ulcers; cobblestoning or nodularity of the bowel; stricture of the bowel associated with oedema, ulceration, or erythema of the mucosa; pseudopolyps; or mucosal bridging 3. **Adverse events**

	4. **Withdrawal due to adverse events**	
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: Based on a review of retrospective studies in the literature, it was estimated that the symptomatic recurrence rate in the control group would be 12.5% per year. Using a sample size calculation based on survival analysis for 2 independent groups with censoring, it was estimated that 178 participants would have to be accrued during a period of 3 years and followed up for a maximum of 6 years to detect a 50% decrease in recurrence (6.25% per year) in the treatment group with a one-tail α of 0.05 and power of 0.80	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization scheme was computer generated by the Clinical Research Support Unit, University of Toronto, and maintained by the pharmacies at the Toronto Hospital, General Division, and St. Mary's Hospital, Rochester" Comment: computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Quote: "All investigators and patients were blinded with respect to treatment allocation" Comment: no further details provided, however the authors confirmed on 27 November 2009 that a central allocation was done by pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects in the control group took six identical-looking placebo tablets twice daily" Comment: participants and investigators were blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patient records were reviewed by an adjudication committee of five investigators (R.S.M., B.G.W., A.H.S., P.W.C., and K.O.) blinded to patient treatment allocation." And "The charts of patients who were noncompliant were reviewed by two blinded gastroenterologists (A.H.S. and P.W.C.), who determined whether noncompliance was secondary to adverse effects potentially related to the medication"

McLeod 1995 (*Continued*)

		Comment: blinding of assessors performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were low, and reasons for withdrawal were balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in methods section were reported
Other bias	Low risk	Quote: "The characteristics of the two groups, which are listed in Table 1, were similar" Comment: groups balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Mowat 2016

Methods	**Study design:** RCT, multicentre **Setting:** UK; 29 secondary and tertiary hospitals; 2008 to 2012
Participants	**Inclusion:** Patients aged at least 16 years (Scotland) or 18 years (England and Wales) with a diagnosis of Crohn's disease and an ileocolic or small bowel resection within the preceding 3 months were eligible for inclusion. Patients successfully treated for a malignancy and in remission for at least 5 years were also eligible **Exclusion:** Residual active Crohn's disease present after surgery, known intolerance or hypersensitivity to thiopurines, known need for further surgery, strictureplasty alone, formation of a stoma, active or untreated malignancy, absent thiopurine methyltransferase activity, substantial abnormalities of liver function tests or full blood count, and pregnancy. Patients receiving treatment for active Crohn's disease at random allocation **Age (IG1/IG2) mean (SD):** 38.76 ± 13.1 overall; 39.2 ± 12.08 vs 38.21 ± 13.4 **Sex (M:F):** 94:146 overall; (49:79) vs (45:67) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** ≤ 3 months **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 240):** 128/112 **Number analysed (n = 240):** (128/128) vs (112/112) **Postrandomisation exclusion (n = 56)**: abnormal blood test results 18 (12/6); early withdrawal 21 (8/13); loss to follow-up 16 (8/7); death 1 (0/1)
Interventions	**Group 1:** Once-daily oral mercaptopurine, at a dose of 1 mg/kg body weight rounded to the nearest 25 mg. Participants with low thiopurine methyltransferase activity were prescribed half the normal dose for 3 years **Group 2:** Identical matched placebo for 3 years **All participants:** Blood monitoring was done weekly for the first 6 weeks and thereafter

	at 6-weekly intervals. Participants with abnormal results had a dose reduction, temporary cessation, or cessation as per a study algorithm. At each study visit, the following data were collected: CDAI, physical examination, concomitant medications, and patient-reported outcomes, including the IBDQ
Outcomes	**Duration of study:** 3 years 1. **Clinical recurrence** defined as CDAI score of over 150 and a 100-point increase from baseline AND the need for anti-inflammatory rescue treatment or primary surgical intervention (ITT calculated as: number that discontinued trial) 2. **Secondary endpoint of clinical recurrence** defined as reaching either of the individual components of the primary outcome (i.e. either a CDAI score of > 150 and a 100-point increase from baseline OR the need for anti-inflammatory rescue treatment or primary surgical intervention) 3. **Endoscopic relapse** defined as a Rutgeerts score of ≥ i2 4. **Crohn's Disease Endoscopic Index of Severity** 5. **Health-related quality of life** 6. **Adverse events** 7. **Severe adverse events** 8.**Withdrawal due to adverse events**
Notes	**Funding source:** Funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. They had no role in the study design, data collection, data analysis, data interpretation, or writing of the report **Conflict of interest:** Authors declare no conflicting interests. **Power calculation**: A sample size of 234 participants was needed to give 80% power to detect a reduction in the frequency of recurrence from 50% in the placebo group to 30% in the treatment group by 3 years at the 5% level of significance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned (1:1) to mercaptopurine or identical matched placebo using a computer-generated web-based randomisation system managed by the Edinburgh Clinical Trials Unit (University of Edinburgh, Edinburgh, UK)" Comment: computer-generated web-based random sequence
Allocation concealment (selection bias)	Low risk	Quote: "Patients' details were entered into the randomisation system before random allocation and were concealed at randomisation" Comment: web-based central allocation

Mowat 2016 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients and their carers and physicians were masked to the treatment allocation" Comment: the study is placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blood monitoring results were reviewed by an independent central clinician masked to treatment allocation and to mean corpuscular volume results. To protect masking, investigators were informed that sham dose reductions were planned for patients on placebo. However, on the advice of the data monitoring committee, sham dose reductions did not occur; the investigators were not informed of this" Comment: outcome assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Analyses were by intention to treat" Comment: attrition rate of 23% when compared with the event risk (30%) was not considered sufficient to lead to bias
Selective reporting (reporting bias)	Low risk	Trial registration available (ISRCTN89489788), and all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "Baseline characteristics were similar between study groups" Comment: groups well balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Prantera 2002

Methods	**Study design:** RCT, single-centre **Setting:** Italy; 1998 to 2000
Participants	**Inclusion:** Eligible patients were aged at least 18 years and were scheduled for curative resection for Crohn's disease. Inclusion criteria were: a diagnosis of Crohn's disease, defined by the criteria adopted by Lennard-Jones and confirmed by surgical specimens; complete resection of all diseased intestine, as shown by inspection at surgery; ability to start oral nutrition and therefore the trial itself within 10 days of operation; and informed written consent

	Exclusion: Exclusion criteria were: pregnancy and lactation; postoperative septic complications; presence of other concomitant important disease; active perianal disease; presence of Crohn's disease in other intestinal tracts; need for antibiotics for more than 10 days after surgery; intake of steroids for more than 30 days after operation; total parenteral nutrition or elemental diet; and use of other drugs possibly active in Crohn's disease. Antidiarrhoeals such as loperamide or other opiates and colestyramine were allowed provided their use had been calculated in the CDAI **Age (IG1/IG2) mean (range):** Not reported, overall > 18; 37.3 (22 to 71) vs 36.2 (22 to 64) **Sex (M:F):** 29:16 overall; (14:9) vs (15:7) **Type of surgery:** not reported **Previous surgery (IG1 + IG2):** 11 (5/6) **Start of intervention after surgery:** ≤ 10 days **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** 16 (10/6) **Number randomised (n = 45):** 23/22 **Number analysed (n = 45):** (23/23) vs (22/22) **Postrandomisation exclusion (n = 8)**: (5/23) vs (3/22) (protocol violation 5 (3/2); dropout 3 (2/1))
Interventions	**Group 1:** LGG (Dicoflor 60; Dicofarm, Rome, Italy) consisted of 2.46-gram bags each containing LGG 6 billion CFU and was administered at a dose of 6 billion CFU twice daily. LGG belongs to *Lactobacillus casei* subspecies *rhamnosus,* isolated by Goldin and Gorbach. **Group 2:** Placebo consisted of bags of identical appearance to the probiotic. Each bag contained maltodextrines 2.060 mg, sorbitol 400 mg, and silicon dioxide 5 mg. The taste and smell of the active substance and placebo were the same **All participants:** The study drugs were administered orally, 1 bag twice daily, morning and afternoon, dissolved in half a glass of water, for 52 weeks. Treatment was started as soon as participants could take solid food by mouth after operation but not later than 10 days after surgery. Follow-up visits were carried out after 13, 26, 39, and 52 weeks of treatment. Compliance with the study drugs was checked by the investigator by counting the number of bags returned at each visit. Treatment failure during the study period was defined as the appearance of Crohn's disease symptoms and/or signs that needed additional medical treatment or operation
Outcomes	**Duration of study:** 52 weeks 1. **Clinical recurrence** defined as increase in CDAI to more than 150 points, confirmed by endoscopic signs of inflammation 2. **Endoscopic relapse** defined as a Rutgeerts score of ≥ i2 3. **Adverse events** 4. **Serious adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation:** Not reported
Risk of bias	

Prantera 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using computerised randomisation in blocks of two, patients were allocated to receive bags of either Dicoflor 60 or placebo" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebo consisted of bags of identical appearance to the probiotic [...] The taste and smell of the active substance and placebo were the same" Comment: trial was reportedly double-blinded and placebo controlled; probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition balanced, all participants accounted for, withdrawals and reasons reported
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.
Other bias	Low risk	Quote: "Demographic and disease characteristics did not differ significantly between the two groups but a higher percentage of patients treated with LGG were smokers" Comment: groups balanced at baseline, except for 1 characteristic. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Regueiro 2009

Methods	**Study design:** RCT, single-centre **Setting:** USA, University of Pittsburgh Medical Center; 2005 to 2007
Participants	**Inclusion:** Participants underwent ileocolonic resection with primary anastomosis **Exclusion:** Exclusion criteria included the following: 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 **Age (IG1/IG2) median:** Overall not reported; 43 vs 32 **Sex (M:F):** 16:8 overall; (6:5) vs (10:3) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** One 16 (7/9); two 6 (3/3); three 2 (1/1) **Start of intervention after surgery:** ≤ 4 weeks **Medication use (IG1 + IG2):** Immunomodulator 11 (4/7); MES 5 (1/4) **Smoker (IG1/IG2):** 6 (5/1) **Number randomised (n = 24):** 11/13 **Number analysed (n = 24):** (11/11) vs (13/13) **Postrandomisation exclusion (n = 3)**: (2/11) vs (1/13) (abdominal pain 1 (1/0); significant infusion reaction 1 (1/0); Crohn's disease exacerbation 1 (0/1))
Interventions	**Group 1:** Infliximab - first infusion administered between 2 and 4 weeks from the time of surgical resection and then 2, 6, and every 8 weeks thereafter for 1 year + immunomodulators and 5-ASA as concomitant treatments **Group 2:** Placebo - first infusion administered between 2 and 4 weeks from the time of surgical resection and then 2, 6, and every 8 weeks thereafter for 1 year + immunomodulators and 5-ASA as concomitant treatments **All participants:** No participants received antibiotics in the postoperative setting. Participants on corticosteroids at the time of surgery were weaned off completely by 2 weeks postoperatively. Participants were assessed at each study infusion (weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54), at colonoscopy (weeks 56 to 60 or withdrawal from study), and at the final study visit at week 66. The CDAI was determined at each study visit. In addition, adverse events were ascertained and samples were collected for laboratory evaluations at each visit. Participants were prospectively monitored for adverse events, temporally recorded as "in the immediate postoperative period," defined as any event within 8 weeks of surgery, and those "outside of the immediate postoperative period," defined as any event that occurred more than 8 weeks from surgery
Outcomes	**Duration of study:** 12 months 1. **Clinical recurrence** defined as increase in CDAI to more than 200 points 2. **Endoscopic relapse** defined as a Rutgeerts score of ≥ i2 3. **Histologic recurrence** based on a histologic activity score and the presence of neutrophils. The histology scoring system was modified from D'Haens and colleagues. The maximum score in the grading scheme was 14 per biopsy site 4. **Adverse events in the immediate and outside the immediate postoperative period**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation:** Specifically, with anticipated 1:1 randomisation of 24 participants, and an endoscopic recurrence of 80% in the placebo group, the study provided 80% power (2-sided type I error rate of 0.05) to detect an absolute difference of 59% associated with infliximab therapy (i.e. 80.0% recurrence in the placebo group, 20.7% recurrence in the infliximab group)

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "All 24 patients underwent ileocolonic resection with primary anastomosis and were then randomized to placebo or infliximab" Comment: insufficient information to make judgement. However, email received from authors on 2 August 2018 stating: "The allocation was done by the central (university) pharmacy. The randozimation was blocked" Comment: block randomisation performed by a pharmacy
Allocation concealment (selection bias)	Low risk	Quote: "The allocation was done by the central (university) pharmacy. The randozimation was blocked" Comment: central allocation. Email received from authors on 2 August 2018 indicated that "Pharmacy maintained the blind"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Insufficient information to make judgement. However email received from authors on 2 August 2018 stating: "The study drug (infliximab or placebo) was delivered from the pharmacist to the research nurse and was blinded.The only unblinded person was the central pharmacist who did the block allocation for randomization. The study drug was unidentified and all study personnel were not aware of the treatment allocation" Comment: participants and personnel blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A blinded investigator (L.B.) reviewed each patient's video recorded procedure and provided a separate endoscopic score. The colonoscopic video recordings were placed on compact discs that were devoid of patient identifiers (i.e., blinded). At the conclusion of the study, the principal investigator (M.R.) rescored each patient by re-reviewing the video recordings in a random and blinded fashion." And "By using standard biopsy forceps, 6 - 8 biopsy specimens were taken from the neoterminal ileum and assessed blindly by a gastrointestinal pathologist (A.R.S.)"

Regueiro 2009 (*Continued*)

		Comment: all outcome assessors blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: low attrition rates, which were balanced across groups (2/11 vs 1/13)
Selective reporting (reporting bias)	Low risk	Trial registration was available (NCT00688636) , and all proposed outcomes were reported
Other bias	High risk	Quote: "In the infliximab group, there were significantly more active smokers (45.5% vs 7.7%; P .06), and a trend for less concomitant immunomodulators use (36.4 vs 53.8%; P .44) or mesalamine use (9.1% vs 30.8%; P .33). In addition, the median baseline ESR was significantly higher in the infliximab group (40 vs 11; P .004), as was the median CRP concentrations (0.5 vs 0. 1; P .05)" Comment: several significant differences between groups at baseline. There are indications that allocation may not have been truly random
All domain risk of bias	Unclear risk	High

Regueiro 2016

Methods	**Study design:** RCT, multicentre **Setting:** Australia, Austria, Belgium, Canada, the Czech Republic, France, Germany, the Netherlands, Hungary, Italy, Poland, the UK, the USA; 104 centres; 2010 to 2012
Participants	**Inclusion:** Patients (> 18 years) with a confirmed diagnosis of CD who had undergone 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 randomisation. Patients with no evidence of macroscopic CD, no known active CD elsewhere in the gastrointestinal tract, with a baseline CDAI score < 200 and with at least 1 of the following risk factors for disease recurrence: qualifying surgery that was their 2nd intra-abdominal resection within 10 years; 3rd or more intra-abdominal resection; resection for a penetrating CD complication (e.g. abscess or fistula); a history of perianal visualising CD, provided the event had not occurred within 3 months; or smoking 10 or more cigarettes per day for the past year were eligible for randomisations within 45 days of resection **Exclusion:** Qualifying surgery more than 10 years after CD diagnosis and surgery performed for stricturing disease involving < 10 cm of bowel **Age (IG1/IG2) mean (SD):** 36.3 ± 12.96 overall; 37.11 ± 3.49 vs 35.4 ± 12.41 **Sex (M:F):** 158:139 overall; (77:70) vs (81:69)

Regueiro 2016 (*Continued*)

	Type of surgery: Not reported **Previous surgery (IG1 + IG2):** 1 or 2 surgeries 114 (63/51); > 2 surgeries 12 (4/8) **Start of intervention after surgery:** ≤ 45 days **Medication use (IG1 + IG2):** Any CD medication 280 (136/144); anti-TNF 67 (37/30); adalimumab 38 (21/17); infliximab 33 (18/15); certolizumab 3 (3/0) **Smoker (IG1/IG2):** Not reported **Number randomised (n = 297):** 147/150 **Number analysed (n = 296):** (146/147) vs (150/150) **Postrandomisation exclusion (n = 77)**: (45/147) vs (32/150) (lost to follow-up 12 (3/9); withdrew consent 41 (26/15); death 1 (0/1); other 23 (16/7))
Interventions	**Group 1:** Infliximab (Remicade; Janssen Biotech Inc, Horsham Township, PA, USA) 5 mg/kg every 8 weeks + continued stable doses of 5-ASA and immunosuppressives post-surgery **Group 2:** Placebo every 8 weeks + continued stable doses of 5-ASA and immunosuppressives postsurgery **All participants:** Participants receiving oral MES or immunosuppressives (AZA, 6-MP, or methotrexate) pre-surgery could continue treatment with maintenance of stable doses after resection. Participants not receiving these agents pre-surgery could not receive them postsurgery. Rectal MES was discontinued at least 2 weeks before randomisation. Initiation of corticosteroids or antibiotics for CD treatment was prohibited
Outcomes	**Duration of study:** 104 weeks 1. **Endoscopic relapse** by ileocolonoscopy defined by a Rutgeerts score ≥ i2 or presence of an abscess, fistula recurrence or development, or treatment failure 2. **Endoscopic recurrence** before or at week 76 defined by endoscopic Rutgeerts score ≥ i2 only 4. **Adverse events**
Notes	**Funding source:** Funded by Jensen Research & Development **Conflict of interest:** Declared for each author; mainly consulting fees, advisory board member fees, speakers, small research grants, etc **Power calculation**: In a study conducted with a patient population similar to that proposed for this study, approximately 40% of participants in the placebo group experienced clinical recurrence by week 52. For calculation of sample size, 50% and 30% of placebo- and infliximab-treated participants, respectively, were expected to develop clinical recurrence by week 76. A sample size of 290 participants, 145 per treatment, provided 93% power to detect a 20% between-group difference in clinical recurrence before or at week 76

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized equally to receive infliximab (Remicade; Janssen Biotech, Inc., Horsham Township, PA) 5 mg/kg or placebo every 8 weeks. Randomization was stratified by the number of risk

Regueiro 2016 (*Continued*)

		factors for recurrence (1 or >1) and current use of an immunosuppressive (yes/no)" Comment: stratified randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and infliximab infusions were administered in a blinded manner" Comment: double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement on blinding of personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All randomized patients were included in efficacy analyses according to assigned treatment, regardless of actual treatment received" Comment: however, over 25% of randomised participants withdrew for reasons other than relapse or adverse event. Given that the event risk is 21%, there is lack of clarity as to whether this is sufficient to cause bias
Selective reporting (reporting bias)	Low risk	Trial registration was available (NCT01190839), and all proposed outcomes were reported
Other bias	Low risk	Quote: "Demographics, qualifying characteristics, and risk factors of the 297 randomized patients were similar between treatment groups" Comment: groups were reportedly well balanced at baseline. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Reinisch 2010

Methods	**Study design:** RCT, multicentre **Setting:** Austria, the Czech Republic, Germany, and Israel; 21 centres; 2002 to 2007
Participants	**Inclusion:** Male or female patients aged 18 to 70 years with a diagnosis of CD confirmed by endoscopy and histology were eligible for screening if they had (1) undergone resection of the terminal ileum and partial colectomy with ileocolonic resection for complications

	of ileal CD with construction of an ileocolonic anastomosis in the preceding 6 to 24 months; (2) not experienced clinical recurrence due to CD since resection; and (3) a CDAI score < 200 in the preceding 1 to 2 weeks. Patients with moderate endoscopic recurrence (Rutgeerts grade i2a: > 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions) or severe endoscopic recurrence (i3 to i4: diffuse aphthous ileitis with diffusely inflamed mucosa, or diffuse inflammation with larger ulcers, nodules and/or narrowing) were recruited into the study **Exclusion:** Patients with a short bowel syndrome, an ileocolonic stoma, a thiopurine methyltransferase genotype; patients who had received treatment with immunosuppressant agents (methotrexate, ciclosporin, 6-MP, azathioprine, or 6-thioguanine (6-TG) or anti-TNFa) since resection, corticosteroids or oral antibiotics (e.g. metronidazole or ciprofloxacin) for > 4 weeks since resection, NSAIDs within the preceding 2 weeks (other than paracetamol or low-dose acetylsalicylic acid); patients who currently had strictureplasty (unless the present strictureplasty macroscopically showed no inflammation at the time of the index operation) or had serum creatinine > 130 μmol/L. Patients were excluded if endoscopy revealed no lesions (grade i0), < 5 aphthous lesions (grade i1), and/or if lesions were confined to the ileocolonic anastomosis (i.e. < 1 cm long) (grade i2b). Patients in the last category (grade i2b) were excluded since this presentation is associated with a lower risk of clinical recurrence **Age (IG1/IG2) mean:** 35.8 ± 12.08 overall; 35.5 ± 13.6 vs 36.0 ± 10.7 **Sex (M:F):** 44:34 overall; (24:17) vs (20:17) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 1 or 2 surgeries 114 (63/51); > 2 surgeries 12 (4/8) **Start of intervention after surgery:** 6 to 24 months **Medication use (IG1 + IG2):** MES 54 (28/26); sulfasalazine 5 (4/1); budesonide 22 (9/13); corticosteroids 39 (23/16); AZA 14 (6/8); infliximab 3 (2/1); other 12 (6/6) **Smoker (IG1/IG2):** 37 (17/20) **Number randomised (n = 78):** 41/37 **Number analysed (n = 78):** (41/41) vs (37/37) **Postrandomisation exclusion (n = 9)**: (4/41) vs (5/37) (lack of co-operation 7 (4/3); lack of efficacy 2 (0/2))
Interventions	**Group 1:** AZA 2.0 to 2.5 mg/kg/day (Azafalk 50 mg tablets) + placebo MES tablets **Group 2:** MES 4 g/day (Eudragit L-coated 500 mg tablets (Salofalk)) + placebo AZA tablets **All participants:** Medications prohibited during the study: immunosuppressants other than study drug, allopurinol, oxipurinol, or thiopurinol, AZA-containing or MES-containing drugs other than study drug, anti-TNFa therapy, oral antibiotics for > 4 weeks or more than 3 cycles of 2 weeks, NSAIDs for > 2 weeks, corticosteroids, and cimetidine
Outcomes	**Duration of study:** 52 weeks 1. **Therapeutic failure (clinical relapse)** defined as CDAI score ≥ 200 and an increase of ≥ 60 points from baseline or study drug discontinuation due to lack of efficacy or an intolerable adverse drug reaction (*at 54 weeks, 2 and 3 years) (ITT data were calculated using per-protocol results plus missing data (missing data = randomised minus per protocol)) 2. **Endoscopic recurrence** defined by endoscopic Rutgeerts score ≥ i2 only 3. **Health-related quality of life** based on IBDQ score at 12 months 4. **Adverse events**

	5. Clinical recurrence follow-up defined as a Rutgeerts score between i2 and i4 within 24 months after the 1-year treatment
Notes	**Funding source:** Dr. Falk Pharma GmbH, Freiburg, Germany **Conflict of interest:** WR has received an unrestricted grant from Dr. Falk Pharma. EFS and KRH have received speaker's honoraria. KD, RG, and RM are employees of Dr. Falk Pharma. SA, WP, OS, ML, SB-M, AT, ES, and MS have no conflicts of interest to declare. AT, ES, and MS are supported in part by the Robert Bosch Foundation, Stuttgart, Germany **Power calculation:** The sample size calculation for the primary endpoint estimated that 62 evaluable participants (31 per treatment arm) were needed to have 80% power to detect a difference of 35% in favour of AZA versus MES for the reduction in the 1-year therapeutic failure rate (1-sided α = 0.025). To allow for non-evaluable participants, a population size of 76 participants (38 per treatment arm) was planned *Data from 2 and 3 years were not included in the analysis as treatment lasted for 54 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...a central randomisation was performed via five computer-generated randomisation lists (using the program 'Rancode +' (version 3.6) of IDV, Gauting, Germany), which were generated for the five body weight classes (40-50 kg, 51-60 kg, 61-75 kg, 76-100 kg and 101-128 kg), each in blocks of four, with medication distributed to each centre according to this list" Comment: centralised randomisation in blocks of 4
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To maintain investigator and patient blinding, patients randomised to azathioprine received verum azathioprine tablets and placebo mesalazine tablets; those randomised to mesalazine received verum mesalazine tablets and placebo azathioprine tablets" Comment: a double-blind, double-dummy RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement

Reinisch 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The intention-to-treat (ITT) population was defined as all randomised patients who received 1 dose of study medication" Comment: the ITT population was defined as all randomised participants who had received 1 dose of study medication
Selective reporting (reporting bias)	Low risk	Trial registration available (NCT00946946), and all prespecified outcomes were reported
Other bias	Low risk	Quote: "Baseline characteristics were similar between treatment groups apart from a lower mean CDAI value in the azathioprine cohort (70 vs 102 in the mesalazine arm) and a higher proportion of azathioprine patients with a penetrating disease behaviour (66% vs 43%)" Comment: some differences at baseline; study supported by Falk Pharma but conflict of interest declared. No other apparent sources of bias detected
All domain risk of bias	Low risk	Low/unclear

Rutgeerts 2005

Methods	**Study design:** RCT, multicentre **Setting:** Belgium; 2 centres; time period not reported
Participants	**Inclusion:** Only patients with ileal involvement with or without right colonic disease within 1 week of resection of all macroscopically involved bowel with anastomosis of non-involved ileum to normal colon (ileocolonic anastomosis) were included in the study **Exclusion:** Pure fibrostenotic disease without biologic inflammation, strictureplasties, 2-step resections with temporary ileostoma, or allergy to nitroimidazole antibiotics **Age (IG1/IG2) median (range):** 18 to 70 overall; 35 (26 to 44) vs 30.5 (24 to 41.25) **Sex (M:F):** 36:42 overall; (16:22) vs (20:20) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 21 (12/9) **Start of intervention after surgery:** < 2 weeks **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** 36 (17/19) **Number randomised (n = 80):** 40/40 **Number analysed (n = 78):** (38/40) vs (40/40) **Postrandomisation exclusion (n = 5)**: (4/40) vs (1/40) (withdrew consent 2 (2/0); compliance 2 (2/0); pregnancy 1 (0/1))

Interventions	**Group 1:** Ornidazole (Tiberal; Roche, Basel, Switzerland) 500 mg twice daily **Group 2:** Placebo 500 mg twice daily **All participants:** All other Crohn's disease-related drugs were discontinued at the time of surgery except for glucocorticosteroids. Steroids were tapered after inclusion and were stopped within 1 month of inclusion
Outcomes	**Duration of study:** 12 months treatment, 2 and 3 years follow-up* 1. **Clinical recurrence** defined as the occurrence of symptoms including diarrhoea, abdominal pain, and decreased well-being regarded by experienced clinicians as a relapse of Crohn's disease symptoms. The CDAI at that time needed to be > 250. In addition, clinical recurrence was also diagnosed if reoperation or other Crohn's disease-related therapy was necessary. (Derived from number of relapses plus number of early withdrawal plus number discontinued due to adverse events) 2. **Endoscopic recurrence** based on a barium meal radiograph follow-through performed 1 year after surgery 3. **Radiologic recurrence** based on IBDQ score at 12 months 4. **Adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: We estimated, on the basis of prior recurrence-prevention studies, that 30% of the participants in the placebo group would have clinical recurrence at 1 year. Randomisation of 80 participants would give the study a 1-sided power of 80% to detect an absolute difference of 25% in the primary outcome parameter between study groups *Data from 2 and 3 years follow-up were not included in the analysis as treatment lasted for 54 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This randomized double-blind placebo-controlled trial was conducted at the inflammatory bowel disease centers of the University Hospital and 1 large teaching hospital" Comment: insufficient information to make judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients received either ornidazole (Tiberal; Roche, Basel, Switzerland) 500 mg twice daily or an identical placebo daily for 54 weeks" Comment: study is a placebo controlled and reported as being double-blind

Rutgeerts 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Biopsy samples of the neoterminal ileum were taken and assessed blindly by 2 pathologists (G.D.H. and K.G.)" Comment: samples taken and assessed by assessors blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Intention-to-treat analysis was performed that included all patients who started the medication" Comment: low attrition rates, which were balanced across groups
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were reported
Other bias	High risk	Quote: "There was a significantly longer duration of disease in the ornidazole group than in the placebo group" Comment: 1 observed imbalance at baseline, no other apparent sources of bias detected
All domain risk of bias	Unclear risk	High

Savarino 2013

Methods	**Study design:** RCT, single-centre **Setting:** Italy; University Hospital of Genoa; 2008 to 2010
Participants	**Inclusion:** Adult patients with ileal or ileocolonic CD within 4 weeks of resection of macroscopically diseased bowel with anastomosis between normal ileum and colon **Exclusion:** Patients with more than 10 years of CD requiring first resective surgery for short (10-centimetre) fibrostenotic stricture; macroscopically active disease not resected at the time of surgery; and presence of a stoma **Age (IG1/IG2) median (range):** Not reported, overall > 18; 45 (22 to 66) vs 46 (25 to 65) vs 49 (24 to 69) **Sex (M:F):** 25:26 overall; (8:8) vs (9:8) vs (8:10) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** One 40 (12/15/13); two 9 (3/2/4); three 2 (1/0/1) **Start of intervention after surgery:** 2 to 4 weeks **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** 19 (9/4/6) **Number randomised (n = 51):** 16/17/18 **Number analysed (n = 51):** (16/16) vs (17/17) vs (18/18) **Postrandomisation exclusion (n = 5)**: (1/16) vs (2/17) vs (2/18) (unclear)

Interventions	**Group 1:** ADA subcutaneous injections 160/80 mg at 0 and 2 weeks, followed by 40 mg every 2 weeks for 2 years **Group 2:** AZA (Azafor, Sofar S.P.A., Milan, Italy) at a dose of 2 mg/kg every day for 2 years **Group 3:** MES (Pentasa, Ferring S.P.A., Milan, Italy) at a dose of 3 g/day divided into 3 doses for 2 years **All participants:** Participants on antibiotics or immunomodulators at entry into the study discontinued these medications 12 weeks before surgery. Continuous use of NSAIDs was not allowed during the study. No other medications were prescribed except for occasional tablets of paracetamol or tramadol. Participants were subjected to endoscopy at 12 and 24 months; small bowel enteroclysis or magnetic resonance imaging at 12 and 24 months; physical examination with interviews, together with an extensive battery of blood tests weekly for the first 4 weeks and then every 2 months, and completed an IBDQ at 1 month before surgery and at 12 and 24 months after surgery. The CDAI was determined at each study visit. In addition, adverse events were ascertained at each visit
Outcomes	**Duration of study:** 2 years 1. **Clinical recurrence** defined as a score of ≥ 2 on the clinical recurrence grading scale 1 to 4 proposed by Hanauer and colleagues (derived from author's primary definition of clinical relapse plus number of early withdrawals) 2. **Clinical recurrence** based on CDAI which was calculated for each participant, and recurrence was set in case of a score > 200, whereas clinical remission was defined as a CDAI score of < 150 2. **Endoscopic recurrence** defined by a Rutgeerts score of ≥ i2 3. **Radiologic recurrence** defined as a score of ≥ 2 on the radiographic recurrence grading scale (where 1 indicates normal; 2, mucosal oedema/aphthoid ulcers; 3, linear ulcers/cobblestoning; and 4, strictures/fistulas/inflammatory mass) 4. **Health-related quality of life** 5. **Median Lémann Index** 5. **Adverse events**
Notes	**Funding source:** Supported by research funds of the university **Conflict of interest:** Authors declare no conflict of interest. **Power calculation**: We considered it reasonable to hypothesise an endoscopic recurrence rate of ~ 80% and 15% and a clinical recurrence rate of ~ 65% and 5% for the MES and ADA groups, respectively, at 2 years' follow-up. This estimation has been supported by the results shown in previous trials on postoperative CD relapse. Thus, based on these data, 13 participants per treatment group was found to be sufficient to detect a difference of at least 65% for endoscopic recurrence and 60% for clinical recurrence in favour of the ADA group with a power of 80% (global type I error of 5%). The number of participants in each group was increased to 16 to compensate for an anticipated dropout rate of 15%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "Eligible and consenting patients were assigned randomly using a computer-generated sequence (www. randomizer.org) to a regimen of…" Comment: computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Quote: "Patient allocation was concealed and performed by an independent nurse not involved with the trial" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study is open-label design.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A blinded investigator (P.D.) reviewed each patient's video-recorded procedure and provided a separate endoscopic score" and "At the conclusion of the study, the principal investigator (E.S.) rescored each patient by re-reviewing the video recordings in a random and blinded manner" Comment: assessors were blinded for endoscopic assessments only. However, no information on clinical assessment of relapse
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Statistical analysis was conducted according to the intention-to-treat principle." Comment: The trial had a low attrition rate. Withdrawals and reasons for withdrawals were balanced across groups (1/16 vs 2/17 vs 2/18)
Selective reporting (reporting bias)	Low risk	Trial registration not available, however all outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "Characteristics were similar for sex, age, smoking, duration of CD, disease behavior, disease location, prior medication exposure, including IFX, and prior surgical resection" Comment: groups well balanced at baseline; no other apparent sources of bias detected

Savarino 2013 (*Continued*)

All domain risk of bias	Unclear risk	High

Scapa 2015

Methods	**Study design:** RCT; abstract **Setting:** Tel Aviv, Israel; study period not reported
Participants	**Inclusion:** All CD patients undergoing a first ileocecectomy for inflammatory complications were prospectively recruited to the Post OPerative Adalimumab Recurrence Trial (POPART) **Exclusion:** Not reported **Age (IG1/IG2) median (SD):** overall not reported; 30.5 ± 2.3 vs 34.4 ± 2.5 **Sex (M:F):** Not reported **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** < 45 days **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** 4 (1/3) **Number randomised (n =):** ? **Number analysed (n = 19):** (8/?) vs (11/?) **Postrandomisation exclusion (n = ?)**: Not reported
Interventions	**Group 1:** Thiopurine (6-MP) 1.5 mg/kg/day **Group 2:** Placebo 500 mg twice daily for 54 weeks **All participants:** All participants underwent ileocolonoscopy at 6 and 12 months to assess for endoscopic recurrence as defined by the Rutgeerts score
Outcomes	**Duration of study:** 12 months 1. **Endoscopic recurrence** defined as a Rutgeerts score of i0 to i1, whilst advanced lesions were defined as i2 to i4
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation:** Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to make judgement

Scapa 2015 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Nineteen patients have reached the 24-week time point" Comment: abstract does not report how many were randomised, the number of withdrawals, and no information is provided regarding any adverse event
Selective reporting (reporting bias)	High risk	Trial registration available (NCT01629628), however clinical relapse not reported in the abstract. Authors informed us via correspondence (12 October 2018) that the full trial will be published by the end of 2018. Adverse events were not reported in the abstract
Other bias	Unclear risk	Insufficient information to make judgement
All domain risk of bias	Unclear risk	High

Sutherland 1997

Methods	**Study design:** RCT, multicentre **Setting:** Canada; 31 hospitals/medical centres; 1990 to 1993
Participants	**Inclusion:** Adult patients (18 years and older) with ileal or ileocolonic CD location restrictions not mentioned. CD in remission for 1 month, but at least 2 flare-ups within the last 4 years, 1 within the last 18 months or a recent resection. Remission defined as CDAI < 150 at baseline and no symptoms within last 30 days. No steroid use within a month of study **Exclusion:** CDAI > 150; previous total proctocolectomy, short bowel syndrome, more than 3 resections within 10 years, chronic perianal disease, ulcer colitis, stool positive for pathogens, parasites, or toxins; drug or alcohol abuse, clinically significant hepatic neurological, endocrine, renal, or other major systemic disease that would make implementation or interpretation of the protocol or results difficult; any history of cancer, allergy to aspirin or MES; patients on immunosuppressant therapy within last 90 days, or corticosteroids within last 30 days or MES/metronidazole within last 7 days before resection **Age (IG1/IG2) mean (±SE):** 36.5 (0.7) overall; 29.7 (1.1) vs 29.0 (1.0) **Sex (M:F):** 106:140 overall; (48:70) vs (58:70) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** 2 to 4 weeks **Medication use (IG1 + IG2):** Not reported

	Smoker (IG1/IG2): Not reported **Number randomised (n = 66):** 31/35 (total number randomised is 293, of which 180 had medically induced remission and 65 surgically induced remission; data presented for the latter only) **Number analysed (n = 66):** (31/31) vs (35/35) **Postrandomisation exclusion (n = ?)**: Not presented separately for participants with surgical remission
Interventions	**Group 1:** 3 capsules of 250 mg MES 4 times a day **Group 2:** 3 capsules of 250 mg placebo 4 times a day **All participants:** No steroid, other mesalazine preparations, aspirin or other NSAIDs, immunosuppressives, narcotics except codeine or loperamide, antibiotics for longer than 14 days
Outcomes	**Duration of study:** 12 months 1. **Clinical recurrence** defined as 1st occurrence of a CDAI that was > 150 as well as an absolute value of at least 60 points higher than baseline or where physician diagnosed a flare-up of disease but a full diary card was not available for the calculation of the final CDAI
Notes	**Funding source:** Supported by research funds of the university **Conflict of interest:** Authors declare no conflict of interest. **Power calculation**: It was hypothesised that the relapse rate for MES-treated participants would be 25%. Assuming an α of 0.05 and a β of 0.20 (power of 0.80), a 2-tailed sample size calculation determined that 150 participants were required for each treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed according to a computer generated randomisation scheme by the study sponsor" Comment: computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Quote: "For each patient, the identity of the study medication was concealed in an individual sealed envelope sent with the drug supplies" and "Medication was packaged by the sponsor and dispensed to each centre on coded identical-appearing boxes" Comment: sequentially numbered, identically appearing drug packages
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medication was packaged by the sponsor and dispensed to each centre on coded identical-appearing boxes" Comment: double-blinded, placebo-con-

Sutherland 1997 (*Continued*)

		trolled trial. Probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates were not reported specifically for the subpopulation of interest in our review (surgical group)
Selective reporting (reporting bias)	Low risk	Although adverse event data were not available for the subpopulation of interest in our review (surgical group), all expected outcomes appear to have been reported for the entire population
Other bias	Low risk	"The demographic characteristics and disease milestones for participants are shown in Table 2. There were no significant differences between the MES- and placebo-treated groups." Supported by a grant by Marion Merrell Dow. Author contacted and confirmed that company had no part in the design, analysis, or write-up of the study
All domain risk of bias	Low risk	Low/unclear

Tursi 2014

Methods	**Study design:** RCT, single-centre **Setting:** Italy; 2010 to 2013
Participants	**Inclusion:** Consecutive CD patients who underwent curative ileocolonic resection and were considered to be at high risk of postoperative recurrence were enrolled **Exclusion:** Active perianal disease, the presence of stoma, adverse events during previous therapy with IFX or AZA, age over 70 years, surgical complications, active infectious disease, history of cancer, renal, cardiac, or hepatic failure, history of acute or chronic pancreatitis, severe leukopenia (WBC <3000 µU/mL, lymphocyte count <1000 µU/mL) , and pregnancy **Age (IG1/IG2) mean (range):** 32.5 (20 to 39) overall; 30.5 (20 to 33) vs 34.5 (22 to 39) **Sex (M:F):** 9:11 overall; (5:5) vs (4:6) **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** 7 (4/3) **Start of intervention after surgery:** 4 to 6 weeks **Medication use (IG1 + IG2):** MES 10; previous AZA use 5; previous IFX use 9 **Smoker (IG1/IG2):** 5 (3/2)

	Number randomised (n = 20): 10/10 **Number analysed (n = 20):** (10/10) vs (10/10) **Postrandomisation exclusion (n = 0)**
Interventions	**Group 1:** Infliximab 5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks for 1 year **Group 2:** Adalimumab 160 mg subcutaneously, followed by 80 mg 2 weeks later, and then 40 mg every 2 weeks for 1 year **All participants:** Treatment was started within 4 to 6 weeks after surgery. All participants also received oral metronidazole (500 mg twice daily) for 2 weeks after surgery. No other CD-related drugs were admitted during the study. Participants underwent monthly evaluation by means of laboratory tests, the Harvey-Bradshaw Index, and the adverse event report. Ileocolonoscopy was performed after 6 and 12 months of therapy and video-recorded
Outcomes	**Duration of study:** 12 months 1. **Clinical recurrence** defined as a Harvey-Bradshaw Index ≥ 8 2. **Endoscopic relapse** defined as a Rutgeerts score of ≥ i2 3. **Histologic relapse** assessed by the Geboes grading system for CD 4. **Adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Authors declare no conflict of interest. **Power calculation**: Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized with a simple unblinded 1:1 allocation ratio..." Comment: insufficient information to make judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	This is an open-label pilot study, and blinding was not performed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Five unblinded endoscopists (AT, CZ, GP, RF, and GB) did all the examinations and calculated scores. Two further unblinded endoscopists (WE and MP) separately reviewed videos and in case of discordance a consensus agreement was reached among the two operators" Comment: blinding of outcome assessors was not performed

Tursi 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; all participants completed the trial
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section were reported.
Other bias	Low risk	Quote: "There were no differences between baseline characteristics of the two groups: age, duration of disease, active smokers, previous surgery, disease behavior and location, perianal disease at diagnosis, extra intestinal manifestations" Comment: groups well balanced at baseline, and no other apparent sources of bias detected
All domain risk of bias	Unclear risk	High

Wenckert 1978

Methods	**Study design:** RCT, multicentre **Setting:** Sweden
Participants	**Inclusion:** No age restrictions mentioned. CD of small or large bowel (or both), 1st resection, and supporting histological evidence of active CD in resected specimens. ESR had to return to normal within 6 weeks of operation, no further remission criteria defined. No steroid use allowed **Exclusion:** Treatment with a bypass, doubtful diagnosis, allergy to sulfasalazine (Salazopyrin) or acetylsalicylic acid, abnormal ESR 6 weeks after operation, lack of co-operation, treatment with corticosteroids or immunosuppressive drugs **Age (IG1/IG2) median:** 24.5 overall **Sex (M:F):** 33:33 overall **Type of surgery:** Not reported **Previous surgery (IG1 + IG2):** n/a **Start of intervention after surgery:** 2 to 4 weeks **Medication use (IG1 + IG2):** Not reported **Smoker (IG1/IG2):** Not reported **Number randomised (n = 66):** 32/34 **Number analysed (n = 66):** (32/32) vs (34/34) **Postrandomisation exclusion (n = 4/66)**: (2/32) vs (2/36)
Interventions	**Group 1:** Sulfasalazine (Salazopyrin) 3 g/day for 18 months **Group 2:** Placebo 3 g/day for 18 months **All participants:** Other specific treatment was avoided. Relapse-free participants were observed for 24 months
Outcomes	1. **Relapse** was defined clinically, based on the information from special control charts on the presence/absence of fever, diarrhoea, rectal bleeding, abdominal pain, extra-in-

	testinal manifestations, palpable abdominal masses, fistulae, abscesses, and possible loss of working days. The relapses were not based on index calculation
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The experimental design was double blind multicentre trial with block-randomisation, and no cross-over." Comment: insufficient data to make judgement. However, author contacted and confirmed that block randomisation described was carried out in accordance with established acceptable randomisation methodology
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient data to make judgement. The author was contacted, but was unable to provide further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient data to make judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient data to make judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for those missing; balanced between study groups; reasons for withdrawal unlikely to be related to true outcome
Selective reporting (reporting bias)	Unclear risk	The study includes results for adverse events, but these are not reported clearly enough to permit analysis and a resulting judgement as to risk of bias
Other bias	Unclear risk	Insufficient information to ascertain whether baseline characteristics were balanced
All domain risk of bias	Low risk	Low/unclear

Yoshida 2012

Methods	**Study design:** RCT, single-centre **Setting:** Japan; Hyogo College of Medicine; 2007 to 2011
Participants	**Inclusion:** Patients aged 12 to 65 years, both sexes with illeal or ileocolic CD within 4 weeks after resection **Exclusion:** Concomitant AZA, or 6-MP that had been started within 8 weeks prior to study; concomitant prednisolone; active infection; macroscopically active disease missed during surgery or the presence of abscess; confirmed tuberculosis; or a history of intolerance to IFX **Age (IG1/IG2) mean (range):** 34.8 ± 10.9 overall; 36.9 ± 11.6 vs 32.8 ± 10.2 **Sex (M:F):** 23:8 overall; (11:4) vs (12:4) **Type of surgery:** Ileal resection 10 (4/6); ileocaecal resection 21 (11/10) **Previous surgery (IG1 + IG2):** Not reported **Start of intervention after surgery:** ± 4 weeks **Medication use (IG1 + IG2):** MES 31 (15/16); corticosteroids 3 (2/1); immunomodulators 5 (3/2); IFX 1 (0/1) **Smoker (IG1/IG2):** 6 (3/3) **Number randomised (n = 31):** 15/16 **Number analysed (n = 31):** (15/15) vs (16/16) **Postrandomisation exclusion (n = 0)**
Interventions	**Group 1:** Infliximab 5 mg/kg intravenously at 8-week intervals (1st infusion 4 weeks after surgery). Also, escalation of the IFX dose above 5 mg/kg/session was avoided + oral MES **Group 2:** Participants could continue with their ongoing conventional medication (oral MES) which had been started longer than 8 weeks prior to surgery **All participants:** In both arms an elemental diet less than 1200 kcal/day was permitted during the study. Oral MES (Pentasa; Kyorin Pharma) was given to participants in both arms at the same mean dosage of 2250 mg/day (range 2250 to 3000), and was continued in all participants at 1500 mg/day during the trial. However, if a participant was to receive AZA, 6-MP, or prednisolone, or to increase the dosage of an ongoing medication, withdrawal from the trial was considered. Together with the clinical evaluations, all participants received ileocolonoscopy to assess mucosal disease activity at 12 months
Outcomes	**Duration of study:** 36 months 1. **Clinical recurrence (CDAI score)** considered if a participant required another medication or to increase the dosage of an ongoing intervention due to worsening CD based on score CDAI > 150 2. **Clinical relapse (IOIBD score)** considered if a participant required another medication or to increase the dosage of an ongoing intervention due to worsening CD based on IOIBD ≥ 2 3. **Serologic relapse (based on CRP level)** defined as failing to maintain CRP level < 0.3 mg/dL 4. **Endoscopic relapse** defined as an endoscopic score of ≥ i2 5. **Adverse events**
Notes	**Funding source:** Not reported **Conflict of interest:** Not reported **Power calculation**: A power of 80% and a 2-sided type I error rate of 5% were assumed. The study size was anticipated to be 1:1 randomisation of at least 28 participants (14 in

	each arm) to detect a group difference

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…randomization was done blindly according to a computer-generated scheme with blocks of two (each two patients were randomly assigned to IFX or to control). This was to minimize the risk of unbalanced group size" Comment: computer-generated 1:1 randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done by a statistician at an independent institute" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label pilot study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Endoscopic evaluations were performed using a videoscope (CF260AI; Olympus Optics, Tokyo, Japan) by endoscopists who were blinded. Video recording procedures were independently scored by different endoscopists" Comment: blinding of outcome assessors performed. Insufficient information about clinical assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for, only 1 withdrawal during study, which was due to adverse events
Selective reporting (reporting bias)	Low risk	Trial registration available (UMIN000004427). All outcomes stated in the methods section were reported
Other bias	Low risk	Quote: "There was no significant difference between the two groups with respect to entry demography, including smoking behavior" Comment: groups well balanced at baseline. No other apparent sources of bias detected

Yoshida 2012 (*Continued*)

All domain risk of bias	Unclear risk	High

5-ASA: 5-aminosalicylic acid; 6-MP: 6-mercaptopurine; ADA: adalimumab; AZA: azathioprine; CD: Crohn's disease; CDAI: Crohn's disease activity index; CFU: colony-forming units; CRP: C-reactive protein; ESR: erythrocyte sediment; IBDQ: inflammatory bowel disease questionnaire; IFX: infliximab; IG; intervention group; IOIBD: International Organization for the Study of Inflammatory Bowel Diseases; ITT: intention-to-treat; kcal: kilocalories; MDZ: metronidazole; MES; mesalazine; n/a: not applicable; NSAID: non-steroidal anti-inflammatory drug; RCT: randomised controlled trial; SD: standard deviation SE: standard error; TNF: tumour necrosis factor; TPN: total parenteral nutrition; WBC: white blood cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angelberger 2013	Not an RCT; a post hoc analysis of a subset of participants of an RCT
Armuzzi 2015	Not an RCT; long-term follow-up observational study
Balzola 2010	Not an RCT; commentary
Bodini 2014a	Not an RCT; commentary on Savarino 2013
Bodini 2014b	Not an RCT; commentary on Savarino 2013
Bodini 2015	Not an RCT; commentary on Savarino 2013
Bourreille 2005	Not an RCT; commentary on Hanauer 2004
De Cruz 2012	Wrong study design; partially randomised
De Cruz 2013a	Duplicate of De Cruz 2013b
De Cruz 2013b	Wrong study design; partially randomised
De Cruz 2013c	Wrong study design; partially randomised
De Cruz 2015a	Wrong study design; partially randomised
De Cruz 2015b	Wrong study design; partially randomised
Doherty 2009	Not an RCT; commentary on Regueiro 2009
Dumois 2001	Not an RCT; commentary on Lochs 2000

(*Continued*)

Ewe 1976	Duplicate containing preliminary results of an included study (Ewe 1989)
Ewe 1980	Not an RCT
Ewe 1981	Not an RCT
Ewe 1984	Duplicate containing preliminary results of an included study (Ewe 1989)
Ferrante 2014	Wrong intervention; AZA vs AZA
Ford 2010	Not an RCT; commentary on Reinisch 2010
Herfarth 2014	Not an RCT; editorial
Kamm 2014a	Wrong study design; partially randomised
Kamm 2014b	Wrong intervention; colonoscopy vs no colonoscopy
Kennedy 2015	Not an RCT;
Liao 2009	Wrong intervention; herb
Manship 2015	Not an RCT; commentary on Hanauer 2004 and Ardizzone 2004
Mardini 2005	Not an RCT; commentaries on Hanauer 2004 and Ardizzone 2004
McLeod 1997	Not an RCT; non-randomised follow-up of McLeod 1995
NCT00074542	Wrong intervention; nutritional supplements
NCT01190839	Duplicate of the trial registration (EUCTR2010-018431-18-DE) of an included study (Regueiro 2016), but was terminated by sponsor
NCT01696942	Terminated trial
NCT02247258	Trial was terminated due to slow recruitment.
NCT02255370	Wrong intervention; nutritional supplements
NCT02997059	Terminated trial
Papamichael 2012	Not an RCT
Regueiro 2013	Not an RCT; follow-up of the control group Regueiro 2009
Regueiro 2014	Not an RCT; follow-up of the control group Regueiro 2009

(*Continued*)

Reibetanz 2015	Not an RCT; commentary on De Cruz 2015a
Ren 2013	Wrong intervention; herb
Sandborn 2004	Not an RCT; editorial
Steinhart 1992	Not an RCT
Tao 2009	Wrong intervention; herb
Vera-Mendoza 2017	Duplicate of Lopez Sanroman 2017
Wright 2014	Wrong intervention; colonoscopy vs no colonoscopy
Wright 2015	Wrong intervention; colonoscopy vs no colonoscopy
Yamamoto 2009	Not an RCT
Yamamoto 2013	Not an RCT; commentary on an excluded study (Papamichael 2012)
Zhu 2015	Wrong intervention; herb

AZA: azathioprine; RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00976690

Methods	RCT
Participants	83 participants Inclusion criteria: • More than 18 years old • Clinical remission at inclusion time (CDAI < 150) • Having ileocolonic or colon resection 21 days before inclusion • Resection > 50 cm or subtotal colectomy with ileorectal anastomosis Exclusion criteria: • Intolerance to 1 or both study treatments • Liver failure (TP < 60%) • Renal failure (creatinine < lab results)
Interventions	1. Azathioprine: 2 mg/kg/day 2. Mesalazine: 4 g/day
Outcomes	Clinically and endoscopically recurrence at 12 and 24 months [Time Frame: 12 and 24 months]

NCT00976690 (*Continued*)

Notes	Under preparation for publication (as informed by authors' response to email from MG) Contact details: LEMANN.marc@lemann.com MG emailed - they are working on the results and preparing publication

NCT01698970

Methods	RCT
Participants	122 participants Inclusion criteria: • Male/female at least 18 years old • Diagnosis of Crohn's disease defined by the criteria usually adopted (Gower-Rousseau 1994) • Crohn's disease mainly limited to the terminal ileum and/or the ascending and transverse colon • Diagnosis of Crohn's disease in agreement with surgical specimen analysis • Patient having given written consent to take part in the study • Complete resection of all main macroscopic ileo-colonic lesions, as shown by inspection at surgery • To have an ileo-colic resection (right, transverse, left) with an anastomosis that can be inspected by endoscopy • Ability to start oral nutrition and therefore the consumption of the study product within 21 days of surgery • Patient receiving no antibiotics at the beginning of the product consumption
Interventions	1. Freeze-dried probiotics provided in capsule (150 mg) containing 1,0 x 10E10 colony forming units per capsule (test)
Outcomes	Recurrent endoscopic ileo-colonic lesions 12 months after surgery
Notes	Danone France (MG contacted Danone UK but they were not able to help)

CDAI: Crohn's disease activity index; RCT: randomised controlled trial; TP: total protein

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2015-000555-24-NL

Trial name or title	Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Determine the Efficacy and Safety of Vedolizumab in Prevention of Endoscopic Recurrence of Crohn's Disease in Patients with Ileo-colonic Surgical Resection and Ileocolonic Anastamosis : REPREVIO (recurrence prevention with Entyvio)
Methods	Randomised, placebo-controlled, double-blind, multicentre study
Participants	Enrolment: 80 participants, 18+ years, both sexes
Interventions	6 months vedolizumab 60 mg vs placebo

EUCTR2015-000555-24-NL (*Continued*)

Outcomes	Primary: endoscopic recurrence (i ≥ 2) Secondary outcomes: 1. The proportion of participants with any endoscopic recurrence of CD (Modified Rutgeerts Grade > i0) after 6 months 2. Changes in the CDAI and Harvey-Bradshaw Index between week 0 and 26. This measure will give an indication for clinical recurrence. Although most participants will remain asymptomatic, we will collect global scores as well as individual components 3. Adverse events and serious adverse events 4. Quality of life measure with a disease-specific instrument (IBDQ) and a generic QoL instrument (SF-36) 5. Serum concentrations of vedolizumab and antibodies to vedolizumab before every infusion
Starting date	October 2016
Contact information	Academic Medical Centre e.clasquin@amc.uva.nl
Notes	

NCT01015391

Trial name or title	Efficacy Study of T2 Versus AZA to Maintain Clinical and Endoscopic Remission in Postoperative Crohn's Disease (T2)
Methods	Randomised, parallel assignment, open-label
Participants	100 participants, 18+ years, with surgically induced remission for CD
Interventions	1 year azathioprine (2.5 mg/kg/d orally until progression or unacceptable toxicity develops the 1st month; 1. 5 mg/kg orally once a day the 2nd month; 2.0 mg/kg orally once a day since the 3rd month; 2.5 mg/kg orally once a day) vs T2 1.5 mg/kg/day orally 3 times a day until progression or unacceptable toxicity develops
Outcomes	Primary: 1. Clinical remission: the proportion of participants with CDAI < 150 at 26 and 52 weeks 2. Endoscopic remission: the proportion of participants with CDEIS < 6 at 26 and 52 weeks Secondary: 1. Time until clinical relapse of CD (CDAI > 150 or an increase of more than 70 points) 2. Time until histological recurrence (determined by biopsies and endoscopic findings) 3. Serum C-reactive protein concentration; erythrocyte sedimentation rate [Time Frame: 52 weeks] 4. The proportion of participants experiencing adverse events
Starting date	April 2009
Contact information	Weiming Zhu, PhD, MD juwiming@yahoo.com.cn
Notes	

NCT02834754

Trial name or title	A Randomized, Double-blind, Placebo Controlled Study of Vedolizumab for the Prevention of Post-operative Crohn's Disease Recurrence
Methods	Randomised, parallel assignment, triple-masking (participant, investigator, outcomes assessor)
Participants	24 participants, 18 years and older, with curative resection and ileocolonic anastomosis for CD
Interventions	52 weeks vedolizumab 300 mg intravenously vs placebo
Outcomes	Primary: endoscopic recurrence (i ≥ 2) Secondary outcome measures: 1. Clinical remission (CDAI < 150) 2. Histologic remission (Geboes score)
Starting date	July 2018
Contact information	Marc B Schwartz, MD mbs53@pitt.edu
Notes	

NCT03185611

Trial name or title	Effectiveness of Rifaximin Combined With Thiopurine on Preventing Postoperative Recurrence in Crohn's Disease
Methods	Parallel randomised trial, single-masking (outcomes assessor)
Participants	80 participants, 18 to 65 years, both sexes; undergoing intestinal resection of all macroscopic diseased bowel, with an endoscopically accessible ileocolic anastomosis with 1 risk factor for developing recurrence in CD
Interventions	6 months after surgery: rifaximin (600 mg, twice daily) + azathioprine (2.0 to 2.5 mg/kg/day) for 3 months after surgery, and then azathioprine monotherapy (2.0 to 2.5 mg/kg/day) for the next 3 months vs azathioprine (2.0 to 2.5 mg/kg/day)
Outcomes	Primary: difference in incidence of endoscopic recurrence (≥ i2) Secondary: adverse events
Starting date	June 2017
Contact information	Xiang Gao, MD, PhD gaoxiangmed@163.com
Notes	

NCT03185624

Trial name or title	Effectiveness of Rifaximin on Preventing Postoperative Recurrence in Crohn's Disease
Methods	Parallel randomised trial, single-masking (outcomes assessor)
Participants	80 participants, 18 to 65 years, both sexes; undergoing intestinal resection of all macroscopic diseased bowel, with an endoscopically accessible ileocolic anastomosis with 1 risk factor for developing recurrence in CD
Interventions	Rifaximin (600 mg, twice daily) for 3 months after surgery vs blank control (no treatment)
Outcomes	Primary: incidence of endoscopic recurrence (≥ i2) Secondary: adverse effect of rifaximin
Starting date	June 2017
Contact information	Xiang Gao, MD, PhD gaoxiangmed@163.com
Notes	

NCT03456752

Trial name or title	The Impact of Perioperative Dexamethasone on Postoperative Outcome in Inflammatory Bowel Diseases
Methods	Randomised, parallel assignment, triple-masking (participant, investigator, outcomes assessor)
Participants	302 participants; 18 to 75 years; CD
Interventions	1 year dexamethasone 8 mg vs placebo (saline solution)
Outcomes	Primary: prolonged ileus Secondary: postoperative nausea and vomiting, postoperative fatigue score, GI-2 recovery, blood count, CRP, interleukin-6, procalcitonin, body composition, mortality, surgical site infections, cost
Starting date	March 2018
Contact information	Jianfeng Gong, MD gongjianfeng@aliyun.com
Notes	

NL6213 (NTR6385)

Trial name or title	Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Determine the Efficacy and Safety of Vedolizumab in Prevention of Endoscopic Recurrence of Crohn's Disease in Patients with Ileo-colonic Surgical Resection and Ileocolonic Anastamosis
Methods	Randomised, parallel, double-blind
Participants	40 participants, age 18+

NL6213 (NTR6385) (*Continued*)

Interventions	1 year vedolizumab 300 mg 8 weekly (4 doses) or placebo 8 weekly (4 doses)
Outcomes	Primary: • Clinically significant endoscopic recurrence (Rutgeerts i2b, i3, or i4) at week 26 Secondary: • Proportion of participants without endoscopic recurrence (i0) • Symptomatic recurrence (CDAI increase > 70 points compared to baseline) • Proportion of participants with normalised serum CRP at all time points and CRP at all visits • Proportion of participants with normal faecal calprotectin (< 50) at all visits • Quality of life measured by IBDQ and SF-36 • Serum concentrations of vedolizumab and antibodies to vedolizumab before every infusion
Starting date	April 2017
Contact information	Prof Dr D'Haens Academic Medical Centre Amsterdam
Notes	

CD: Crohn's disease; CDAI: Crohn's disease activity index; IBDQ: inflammatory bowel disease questionnaire; QoL: quality of life; SF-36: short form-36; AZA: azathioprine; CDEIS: Crohn's disease endoscopic index of severity; GI-2: gastrointestinal - 2; CRP: C-reactive protein

DATA AND ANALYSES

Comparison 1. Direct evidence: 5-ASA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	5	671	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.72, 0.98]
2 Adverse events	4	407	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.81, 3.43]
3 Serious adverse events	2	408	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.34, 1.87]
4 Withdrawal due to adverse events	3	320	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.71, 3.94]
5 Endoscopic relapse	2	450	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.15]

Comparison 2. Direct evidence: 5-ASA versus adalimumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	34	Risk Ratio (M-H, Fixed, 95% CI)	8.0 [1.13, 56.41]
2 Adverse events	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.75, 1.71]
3 Endoscopic relapse	1	34	Risk Ratio (M-H, Fixed, 95% CI)	13.33 [1.98, 89.95]
4 Withdrawal due to adverse events	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [0.12, 61.58]

Comparison 3. Direct evidence: 5-ASA versus purine analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	4	347	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.11]
2 Adverse events	4	347	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.87, 1.36]
3 Serious adverse events	2	233	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.83, 4.07]
4 Withdrawal due to adverse events	4	347	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.31, 0.92]
5 Endoscopic relapse	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.86, 1.94]

Comparison 4. Direct evidence: antibiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.38]
2 Adverse events	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.16]
3 Withdrawal due to adverse events	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 1.89]
4 Endoscopic relapse	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.68, 1.07]

Comparison 5. Direct evidence: budesonide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.40, 1.18]
2 Adverse events	2	213	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.27]
3 Withdrawal due to adverse events	2	210	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.35, 3.14]
4 Histologic relapse	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.12]

Comparison 6. Direct evidence: infliximab versus adalimumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 13.87]
2 Adverse events	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Endoscopic relapse	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.21, 18.69]
4 Histologic relapse	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.32, 7.14]

Comparison 7. Direct evidence: infliximab versus purine analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.75]
2 Withdrawal due to adverse events	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.39]
3 Endoscopic relapse	1	22	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.05]
4 Histologic relapse	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.06, 0.80]

Comparison 8. Direct evidence: probiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.46]
2 Adverse events	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.07, 1.41]
3 Endoscopic relapse	3	213	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.25]

Comparison 9. Direct evidence: purine analogues versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	2	327	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.69, 0.96]
2 Adverse events	1	87	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.64, 5.75]
3 Serious adverse events	2	327	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.30, 3.94]
4 Withdrawal due to adverse events	2	327	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.66, 1.30]
5 Endoscopic relapse	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.11]

Comparison 10. Direct evidence: purine analogues versus adalimumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	33	Risk Ratio (M-H, Fixed, 95% CI)	11.29 [1.65, 77.22]
2 Adverse events	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.81, 1.78]
3 Withdrawal due to adverse events	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [0.12, 64.89]
4 Endoscopic relapse	2	52	Risk Ratio (M-H, Fixed, 95% CI)	8.17 [2.01, 33.25]

Comparison 11. Direct evidence: sulfasalazine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.24, 1.38]
2 Adverse events	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.38]
3 Withdrawal due to adverse events	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.38]

Comparison 12. Direct evidence: sulfasalazine + prednisolone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical relapse	1	97	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.57, 2.40]

Comparison 13. Direct evidence not in network: clinical relapse

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4.0 g/d versus 2.4 g/d mesalazine	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.37, 1.08]
2 Purine analogues versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Infliximab versus placebo	2	53	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.16, 1.33]
4 Antibiotics versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 5-ASA versus purine analogues	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.47]

Comparison 14. Direct evidence not in network: adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4.0 g/d versus 2.4 g/d mesalazine	1	206	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.24]
2 Probiotics versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Infliximab versus placebo	3	362	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.34, 0.70]
4 5-ASA versus purine analogues	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Purine analogues versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 15. Direct evidence not in network: serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 5-ASA versus purine analogues	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 16. Direct evidence not in network: withdrawal due to adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4.0 g/d versus 2.4 g/d mesalazine	1	206	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.24]
2 Synbiotic versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Probiotics versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Infliximab versus placebo	4	393	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.31, 0.72]
5 5-ASA versus purine analogues	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Purine analogues versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 17. Direct evidence not in network: endoscopic relapse

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 4.0 g/d versus 2.4 g/d mesalazine	1	206	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.60, 1.04]
2 Probiotics versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Infliximab versus placebo	4	395	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.74]
4 5-ASA versus purine analogues	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Purine analogues versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Direct evidence: 5-ASA versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 1 Direct evidence: 5-ASA versus placebo

Outcome: 1 Clinical relapse

Study or subgroup	5-ASA n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brignola 1995	13/44	14/43		6.1 %	0.91 [0.48, 1.70]
Caprilli 1994	20/55	28/55		12.6 %	0.71 [0.46, 1.10]
Hanauer 2004	33/44	35/40		55.7 %	0.86 [0.70, 1.05]
Lochs 2000	47/154	59/170		24.0 %	0.88 [0.64, 1.21]
Sutherland 1997	3/31	8/35		1.6 %	0.42 [0.12, 1.46]
Total (95% CI)	**328**	**343**		**100.0 %**	**0.84 [0.72, 0.98]**

Total events: 116 (5-ASA), 144 (placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.95$, df = 4 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 2.26 (P = 0.024)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Direct evidence: 5-ASA versus placebo, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 1 Direct evidence: 5-ASA versus placebo

Outcome: 2 Adverse events

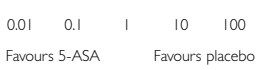
Study or subgroup	5-ASA n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Brignola 1995	5/44	3/43		28.0 %	1.63 [0.41, 6.40]
Caprilli 1994	2/55	0/55		4.6 %	5.00 [0.25, 101.81]
Florent 1996	5/65	3/61		28.6 %	1.56 [0.39, 6.27]
Hanauer 2004	6/44	4/40		38.7 %	1.36 [0.41, 4.48]
Total (95% CI)	**208**	**199**		**100.0 %**	**1.66 [0.81, 3.43]**

Total events: 18 (5-ASA), 10 (placebo)

Heterogeneity: $Chi^2 = 0.63$, df = 3 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 1.38 (P = 0.17)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Direct evidence: 5-ASA versus placebo, Outcome 3 Serious adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 1 Direct evidence: 5-ASA versus placebo

Outcome: 3 Serious adverse events

Study or subgroup	5-ASA n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hanauer 2004	0/44	2/40		23.4 %	0.18 [0.01, 3.68]
Lochs 2000	8/154	9/170		76.6 %	0.98 [0.39, 2.48]
Total (95% CI)	**198**	**210**		**100.0 %**	**0.79 [0.34, 1.87]**

Total events: 8 (5-ASA), 11 (placebo)

Heterogeneity: Chi^2 = 1.12, df = 1 (P = 0.29); I^2 =11%

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Direct evidence: 5-ASA versus placebo, Outcome 4 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 1 Direct evidence: 5-ASA versus placebo

Outcome: 4 Withdrawal due to adverse events

Study or subgroup	5-ASA n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caprilli 1994	2/55	0/55		6.4 %	5.00 [0.25, 101.81]
Florent 1996	5/65	3/61		39.8 %	1.56 [0.39, 6.27]
Hanauer 2004	6/44	4/40		53.8 %	1.36 [0.41, 4.48]
Total (95% CI)	**164**	**156**		**100.0 %**	**1.68 [0.71, 3.94]**

Total events: 13 (5-ASA), 7 (placebo)

Heterogeneity: Chi^2 = 0.63, df = 2 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 1.19 (P = 0.24)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Direct evidence: 5-ASA versus placebo, Outcome 5 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 1 Direct evidence: 5-ASA versus placebo

Outcome: 5 Endoscopic relapse

Study or subgroup	5-ASA n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Florent 1996	38/65	40/61		24.5 %	0.89 [0.68, 1.17]
Lochs 2000	133/154	134/170		75.5 %	1.10 [0.99, 1.21]
Total (95% CI)	**219**	**231**		**100.0 %**	**1.05 [0.95, 1.15]**
Total events: 171 (5-ASA), 174 (Placebo)					
Heterogeneity: Chi^2 = 2.14, df = 1 (P = 0.14); I^2 =53%					
Test for overall effect: Z = 0.88 (P = 0.38)					
Test for subgroup differences: Not applicable					

Analysis 2.1. Comparison 2 Direct evidence: 5-ASA versus adalimumab, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 2 Direct evidence: 5-ASA versus adalimumab

Outcome: 1 Clinical relapse

Study or subgroup	5-ASA n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	9/18	1/16		100.0 %	8.00 [1.13, 56.41]
Total (95% CI)	**18**	**16**		**100.0 %**	**8.00 [1.13, 56.41]**
Total events: 9 (5-ASA), 1 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.037)					
Test for subgroup differences: Not applicable					

Analysis 2.2. Comparison 2 Direct evidence: 5-ASA versus adalimumab, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 2 Direct evidence: 5-ASA versus adalimumab

Outcome: 2 Adverse events

Study or subgroup	5-ASA n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	14/18	11/16		100.0 %	1.13 [0.75, 1.71]
Total (95% CI)	**18**	**16**		**100.0 %**	**1.13 [0.75, 1.71]**
Total events: 14 (5-ASA), 11 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					
Test for subgroup differences: Not applicable					

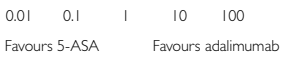
Analysis 2.3. Comparison 2 Direct evidence: 5-ASA versus adalimumab, Outcome 3 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 2 Direct evidence: 5-ASA versus adalimumab

Outcome: 3 Endoscopic relapse

Study or subgroup	5-ASA n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	15/18	1/16		100.0 %	13.33 [1.98, 89.95]
Total (95% CI)	**18**	**16**		**100.0 %**	**13.33 [1.98, 89.95]**
Total events: 15 (5-ASA), 1 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.66 (P = 0.0078)					
Test for subgroup differences: Not applicable					



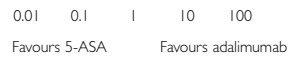
Analysis 2.4. Comparison 2 Direct evidence: 5-ASA versus adalimumab, Outcome 4 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 2 Direct evidence: 5-ASA versus adalimumab

Outcome: 4 Withdrawal due to adverse events

Study or subgroup	5-ASA n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	1/18	0/16		100.0 %	2.68 [0.12, 61.58]
Total (95% CI)	**18**	**16**		**100.0 %**	**2.68 [0.12, 61.58]**
Total events: 1 (5-ASA), 0 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.62 (P = 0.54)					
Test for subgroup differences: Not applicable					



Analysis 3.1. Comparison 3 Direct evidence: 5-ASA versus purine analogues, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 3 Direct evidence: 5-ASA versus purine analogues

Outcome: 1 Clinical relapse

Study or subgroup	5-ASA n/N	purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	32/71	35/71		32.1 %	0.91 [0.65, 1.30]
Hanauer 2004	33/44	32/47		28.3 %	1.10 [0.85, 1.43]
Herfarth 2006	27/37	33/42		28.3 %	0.93 [0.72, 1.19]
Savarino 2013	9/18	12/17		11.3 %	0.71 [0.41, 1.23]
Total (95% CI)	**170**	**177**		**100.0 %**	**0.95 [0.81, 1.11]**

Total events: 101 (5-ASA), 112 (purine analogues)

Heterogeneity: $Chi^2 = 2.41$, df = 3 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Direct evidence: 5-ASA versus purine analogues, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 3 Direct evidence: 5-ASA versus purine analogues

Outcome: 2 Adverse events

Study or subgroup	5-ASA n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	27/71	18/71		26.4 %	1.50 [0.91, 2.47]
Hanauer 2004	6/44	9/47		12.7 %	0.71 [0.28, 1.84]
Herfarth 2006	26/37	29/42		39.8 %	1.02 [0.76, 1.36]
Savarino 2013	14/18	14/17		21.1 %	0.94 [0.68, 1.31]
Total (95% CI)	**170**	**177**		**100.0 %**	**1.09 [0.87, 1.36]**

Total events: 73 (5-ASA), 70 (Purine analogues)

Heterogeneity: $Chi^2 = 3.30$, df = 3 (P = 0.35); $I^2 = 9\%$

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Direct evidence: 5-ASA versus purine analogues, Outcome 3 Serious adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 3 Direct evidence: 5-ASA versus purine analogues

Outcome: 3 Serious adverse events

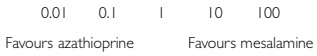
Study or subgroup	Azathioprine n/N	Mesalamine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	15/71	6/71		71.3 %	2.50 [1.03, 6.07]
Hanauer 2004	0/44	2/47		28.7 %	0.21 [0.01, 4.32]
Total (95% CI)	**115**	**118**		**100.0 %**	**1.84 [0.83, 4.07]**

Total events: 15 (Azathioprine), 8 (Mesalamine)

Heterogeneity: $Chi^2 = 2.43$, df = 1 (P = 0.12); $I^2 = 59\%$

Test for overall effect: Z = 1.51 (P = 0.13)

Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3 Direct evidence: 5-ASA versus purine analogues, Outcome 4 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 3 Direct evidence: 5-ASA versus purine analogues

Outcome: 4 Withdrawal due to adverse events

Study or subgroup	5-ASA n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ardizzone 2004	6/71	15/71		47.2 %	0.40 [0.16, 0.97]
Hanauer 2004	6/44	9/47		27.4 %	0.71 [0.28, 1.84]
Herfarth 2006	4/37	7/42		20.6 %	0.65 [0.21, 2.04]
Savarino 2013	0/18	1/17		4.8 %	0.32 [0.01, 7.26]
Total (95% CI)	**170**	**177**		**100.0 %**	**0.53 [0.31, 0.92]**

Total events: 16 (5-ASA), 32 (Purine analogues)

Heterogeneity: $Chi^2 = 0.98$, df = 3 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 2.24 (P = 0.025)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Direct evidence: 5-ASA versus purine analogues, Outcome 5 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 3 Direct evidence: 5-ASA versus purine analogues

Outcome: 5 Endoscopic relapse

Study or subgroup	5-ASA n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	15/18	11/17		100.0 %	1.29 [0.86, 1.94]
Total (95% CI)	**18**	**17**		**100.0 %**	**1.29 [0.86, 1.94]**

Total events: 15 (5-ASA), 11 (Purine analogues)
Heterogeneity: not applicable
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Direct evidence: antibiotics versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 4 Direct evidence: antibiotics versus placebo

Outcome: 1 Clinical relapse

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herfarth 2013	10/17	8/16		29.2 %	1.18 [0.63, 2.21]
Rutgeerts 2005	17/40	20/40		70.8 %	0.85 [0.53, 1.37]
Total (95% CI)	**57**	**56**		**100.0 %**	**0.95 [0.65, 1.38]**

Total events: 27 (Antibiotics), 28 (Placebo)
Heterogeneity: Chi^2 = 0.65, df = 1 (P = 0.42); I^2 =0.0%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Direct evidence: antibiotics versus placebo, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 4 Direct evidence: antibiotics versus placebo

Outcome: 2 Adverse events

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herfarth 2013	1/17	6/16		100.0 %	0.16 [0.02, 1.16]
Total (95% CI)	**17**	**16**		**100.0 %**	**0.16 [0.02, 1.16]**
Total events: 1 (Antibiotics), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.070)					
Test for subgroup differences: Not applicable					

Analysis 4.3. Comparison 4 Direct evidence: antibiotics versus placebo, Outcome 3 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 4 Direct evidence: antibiotics versus placebo

Outcome: 3 Withdrawal due to adverse events

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herfarth 2013	1/17	4/16		100.0 %	0.24 [0.03, 1.89]
Total (95% CI)	**17**	**16**		**100.0 %**	**0.24 [0.03, 1.89]**
Total events: 1 (Antibiotics), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.36 (P = 0.17)					
Test for subgroup differences: Not applicable					

Analysis 4.4. Comparison 4 Direct evidence: antibiotics versus placebo, Outcome 4 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 4 Direct evidence: antibiotics versus placebo

Outcome: 4 Endoscopic relapse

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herfarth 2013	11/17	11/16		25.6 %	0.94 [0.58, 1.52]
Rutgeerts 2005	27/40	33/40		74.4 %	0.82 [0.63, 1.06]
Total (95% CI)	**57**	**56**		**100.0 %**	**0.85 [0.68, 1.07]**
Total events: 38 (Antibiotics), 44 (Placebo)					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.40 (P = 0.16)					
Test for subgroup differences: Not applicable					

Analysis 5.1. Comparison 5 Direct evidence: budesonide versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 5 Direct evidence: budesonide versus placebo

Outcome: 1 Clinical relapse

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ewe 1999	14/43	19/40		100.0 %	0.69 [0.40, 1.18]
Total (95% CI)	**43**	**40**		**100.0 %**	**0.69 [0.40, 1.18]**
Total events: 14 (Corticosteroids), 19 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Test for subgroup differences: Not applicable					

Analysis 5.2. Comparison 5 Direct evidence: budesonide versus placebo, Outcome 2 Adverse events.

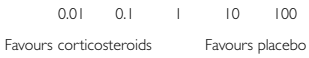
Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 5 Direct evidence: budesonide versus placebo

Outcome: 2 Adverse events

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ewe 1999	13/43	7/40		12.8 %	1.73 [0.77, 3.89]
Hellers 1999	44/63	51/67		87.2 %	0.92 [0.74, 1.13]
Total (95% CI)	**106**	**107**		**100.0 %**	**1.02 [0.82, 1.27]**

Total events: 57 (Corticosteroids), 58 (Placebo)
Heterogeneity: Chi^2 = 2.60, df = 1 (P = 0.11); I^2 =62%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5 Direct evidence: budesonide versus placebo, Outcome 3 Withdrawal due to adverse events.

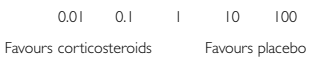
Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 5 Direct evidence: budesonide versus placebo

Outcome: 3 Withdrawal due to adverse events

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ewe 1999	1/40	1/40		17.1 %	1.00 [0.06, 15.44]
Hellers 1999	5/63	5/67		82.9 %	1.06 [0.32, 3.50]
Total (95% CI)	**103**	**107**		**100.0 %**	**1.05 [0.35, 3.14]**

Total events: 6 (Corticosteroids), 6 (Placebo)
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable



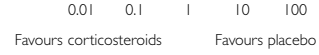
Analysis 5.4. Comparison 5 Direct evidence: budesonide versus placebo, Outcome 4 Histologic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 5 Direct evidence: budesonide versus placebo

Outcome: 4 Histologic relapse

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ewe 1999	36/43	38/43		100.0 %	0.95 [0.80, 1.12]
Total (95% CI)	**43**	**43**		**100.0 %**	**0.95 [0.80, 1.12]**
Total events: 36 (Corticosteroids), 38 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.62 (P = 0.53)					
Test for subgroup differences: Not applicable					



Analysis 6.1. Comparison 6 Direct evidence: infliximab versus adalimumab, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 6 Direct evidence: infliximab versus adalimumab

Outcome: 1 Clinical relapse

Study or subgroup	Infliximab n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tursi 2014	1/10	1/10		100.0 %	1.00 [0.07, 13.87]
Total (95% CI)	**10**	**10**		**100.0 %**	**1.00 [0.07, 13.87]**
Total events: 1 (Infliximab), 1 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

Analysis 6.2. Comparison 6 Direct evidence: infliximab versus adalimumab, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 6 Direct evidence: infliximab versus adalimumab

Outcome: 2 Adverse events

Study or subgroup	Infliximab n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tursi 2014	0/10	0/10			Not estimable
Total (95% CI)	**10**	**10**			**Not estimable**
Total events: 0 (Infliximab), 0 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 6.3. Comparison 6 Direct evidence: infliximab versus adalimumab, Outcome 3 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 6 Direct evidence: infliximab versus adalimumab

Outcome: 3 Endoscopic relapse

Study or subgroup	Infliximab n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tursi 2014	2/10	1/10		100.0 %	2.00 [0.21, 18.69]
Total (95% CI)	**10**	**10**		**100.0 %**	**2.00 [0.21, 18.69]**
Total events: 2 (Infliximab), 1 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Test for subgroup differences: Not applicable					

Analysis 6.4. Comparison 6 Direct evidence: infliximab versus adalimumab, Outcome 4 Histologic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 6 Direct evidence: infliximab versus adalimumab

Outcome: 4 Histologic relapse

Study or subgroup	Infliximab n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tursi 2014	3/10	2/10		100.0 %	1.50 [0.32, 7.14]
Total (95% CI)	**10**	**10**		**100.0 %**	**1.50 [0.32, 7.14]**
Total events: 3 (Infliximab), 2 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
Test for subgroup differences: Not applicable					

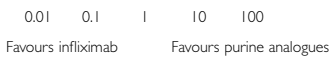
Analysis 7.1. Comparison 7 Direct evidence: infliximab versus purine analogues, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 7 Direct evidence: infliximab versus purine analogues

Outcome: 1 Clinical relapse

Study or subgroup	Infliximab n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Armuzzi 2013	1/11	2/11		100.0 %	0.50 [0.05, 4.75]
Total (95% CI)	**11**	**11**		**100.0 %**	**0.50 [0.05, 4.75]**
Total events: 1 (Infliximab), 2 (Purine analogues)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
Test for subgroup differences: Not applicable					



Analysis 7.2. Comparison 7 Direct evidence: infliximab versus purine analogues, Outcome 2 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 7 Direct evidence: infliximab versus purine analogues

Outcome: 2 Withdrawal due to adverse events

Study or subgroup	Infliximab n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Armuzzi 2013	0/11	1/11		100.0 %	0.33 [0.02, 7.39]
Total (95% CI)	**11**	**11**		**100.0 %**	**0.33 [0.02, 7.39]**
Total events: 0 (Infliximab), 1 (Purine analogues)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					

Analysis 7.3. Comparison 7 Direct evidence: infliximab versus purine analogues, Outcome 3 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 7 Direct evidence: infliximab versus purine analogues

Outcome: 3 Endoscopic relapse

Study or subgroup	Infliximab n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Armuzzi 2013	1/11	1/11		100.0 %	1.00 [0.07, 14.05]
Total (95% CI)	**11**	**11**		**100.0 %**	**1.00 [0.07, 14.05]**
Total events: 1 (Infliximab), 1 (Purine analogues)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

Analysis 7.4. Comparison 7 Direct evidence: infliximab versus purine analogues, Outcome 4 Histologic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 7 Direct evidence: infliximab versus purine analogues

Outcome: 4 Histologic relapse

Study or subgroup	Infliximab n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Armuzzi 2013	2/11	9/11		100.0 %	0.22 [0.06, 0.80]
Total (95% CI)	**11**	**11**		**100.0 %**	**0.22 [0.06, 0.80]**
Total events: 2 (Infliximab), 9 (Purine analogues)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.30 (P = 0.022)					
Test for subgroup differences: Not applicable					

Analysis 8.1. Comparison 8 Direct evidence: probiotics versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 8 Direct evidence: probiotics versus placebo

Outcome: 1 Clinical relapse

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gossum 2007	11/34	17/36		76.4 %	0.69 [0.38, 1.24]
Prantera 2002	8/23	5/22		23.6 %	1.53 [0.59, 3.97]
Total (95% CI)	**57**	**58**		**100.0 %**	**0.88 [0.54, 1.46]**

Total events: 19 (Probiotics), 22 (Placebo)
Heterogeneity: Chi^2 = 1.98, df = 1 (P = 0.16); I^2 =49%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable

Analysis 8.2. Comparison 8 Direct evidence: probiotics versus placebo, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 8 Direct evidence: probiotics versus placebo

Outcome: 2 Adverse events

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Prantera 2002	2/23	6/22		100.0 %	0.32 [0.07, 1.41]
Total (95% CI)	**23**	**22**		**100.0 %**	**0.32 [0.07, 1.41]**

Total events: 2 (Probiotics), 6 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable

Analysis 8.3. Comparison 8 Direct evidence: probiotics versus placebo, Outcome 3 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 8 Direct evidence: probiotics versus placebo

Outcome: 3 Endoscopic relapse

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gossum 2007	28/34	27/36		37.6 %	1.10 [0.86, 1.40]
Marteau 2006	26/48	33/50		46.3 %	0.82 [0.59, 1.14]
Prantera 2002	17/23	11/22		16.1 %	1.48 [0.91, 2.40]
Total (95% CI)	**105**	**108**		**100.0 %**	**1.03 [0.85, 1.25]**

Total events: 71 (Probiotics), 71 (Placebo)

Heterogeneity: Chi^2 = 4.25, df = 2 (P = 0.12); I^2 =53%

Test for overall effect: Z = 0.31 (P = 0.75)

Test for subgroup differences: Not applicable

Analysis 9.1. Comparison 9 Direct evidence: purine analogues versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 9 Direct evidence: purine analogues versus placebo

Outcome: 1 Clinical relapse

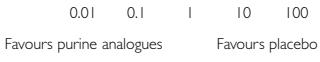
Study or subgroup	Purine analogues n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hanauer 2004	32/47	35/40		33.6 %	0.78 [0.62, 0.98]
Mowat 2016	66/128	70/112		66.4 %	0.83 [0.66, 1.03]
Total (95% CI)	**175**	**152**		**100.0 %**	**0.81 [0.69, 0.96]**

Total events: 98 (Purine analogues), 105 (Placebo)

Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%

Test for overall effect: Z = 2.50 (P = 0.012)

Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9 Direct evidence: purine analogues versus placebo, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 9 Direct evidence: purine analogues versus placebo

Outcome: 2 Adverse events

Study or subgroup	Purine analogues n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hanauer 2004	9/47	4/40		100.0 %	1.91 [0.64, 5.75]
Total (95% CI)	**47**	**40**		**100.0 %**	**1.91 [0.64, 5.75]**
Total events: 9 (Purine analogues), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Not applicable					

Analysis 9.3. Comparison 9 Direct evidence: purine analogues versus placebo, Outcome 3 Serious adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 9 Direct evidence: purine analogues versus placebo

Outcome: 3 Serious adverse events

Study or subgroup	Purine analogues n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hanauer 2004	2/47	2/40		50.3 %	0.85 [0.13, 5.77]
Mowat 2016	3/128	2/112		49.7 %	1.31 [0.22, 7.71]
Total (95% CI)	**175**	**152**		**100.0 %**	**1.08 [0.30, 3.94]**
Total events: 5 (Purine analogues), 4 (Placebo)					
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 0.12 (P = 0.91)					
Test for subgroup differences: Not applicable					

Analysis 9.4. Comparison 9 Direct evidence: purine analogues versus placebo, Outcome 4 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 9 Direct evidence: purine analogues versus placebo

Outcome: 4 Withdrawal due to adverse events

Study or subgroup	Purine analogues n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hanauer 2004	9/47	4/40		9.0 %	1.91 [0.64, 5.75]
Mowat 2016	39/128	41/112		91.0 %	0.83 [0.58, 1.19]
Total (95% CI)	**175**	**152**		**100.0 %**	**0.93 [0.66, 1.30]**
Total events: 48 (Purine analogues), 45 (Placebo)					
Heterogeneity: Chi^2 = 2.03, df = 1 (P = 0.15); I^2 =51%					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 9.5. Comparison 9 Direct evidence: purine analogues versus placebo, Outcome 5 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 9 Direct evidence: purine analogues versus placebo

Outcome: 5 Endoscopic relapse

Study or subgroup	Purine analogues n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mowat 2016	90/128	83/112		100.0 %	0.95 [0.81, 1.11]
Total (95% CI)	**128**	**112**		**100.0 %**	**0.95 [0.81, 1.11]**
Total events: 90 (Purine analogues), 83 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Not applicable					

Analysis 10.1. Comparison 10 Direct evidence: purine analogues versus adalimumab, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 10 Direct evidence: purine analogues versus adalimumab

Outcome: 1 Clinical relapse

Study or subgroup	Purine analogues n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	12/17	1/16		100.0 %	11.29 [1.65, 77.22]
Total (95% CI)	**17**	**16**		**100.0 %**	**11.29 [1.65, 77.22]**
Total events: 12 (Purine analogues), 1 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.47 (P = 0.013)					
Test for subgroup differences: Not applicable					

Analysis 10.2. Comparison 10 Direct evidence: purine analogues versus adalimumab, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 10 Direct evidence: purine analogues versus adalimumab

Outcome: 2 Adverse events

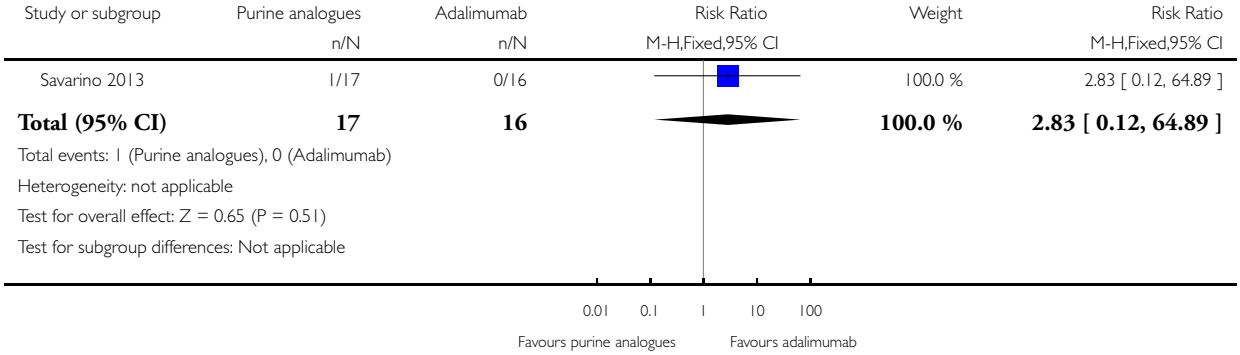
Study or subgroup	Purine analogues n/N	Adalimumab n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Savarino 2013	14/17	11/16		100.0 %	1.20 [0.81, 1.78]
Total (95% CI)	**17**	**16**		**100.0 %**	**1.20 [0.81, 1.78]**
Total events: 14 (Purine analogues), 11 (Adalimumab)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.37)					
Test for subgroup differences: Not applicable					

Analysis 10.3. Comparison 10 Direct evidence: purine analogues versus adalimumab, Outcome 3 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 10 Direct evidence: purine analogues versus adalimumab

Outcome: 3 Withdrawal due to adverse events

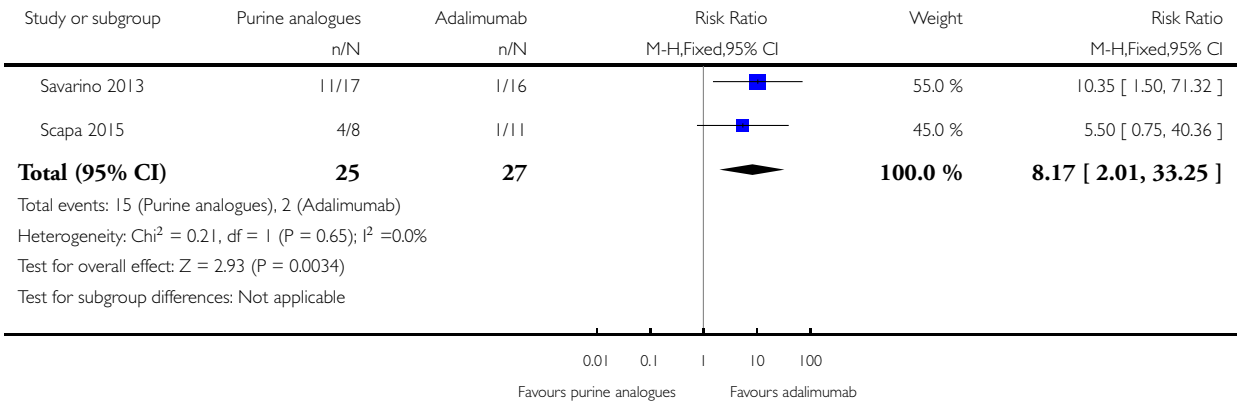


Analysis 10.4. Comparison 10 Direct evidence: purine analogues versus adalimumab, Outcome 4 Endoscopic relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 10 Direct evidence: purine analogues versus adalimumab

Outcome: 4 Endoscopic relapse



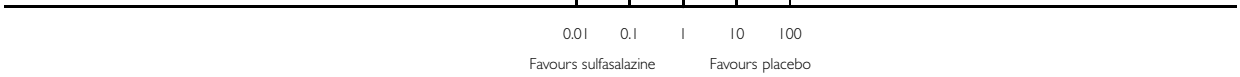
Analysis 11.1. Comparison 11 Direct evidence: sulfasalazine versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 11 Direct evidence: sulfasalazine versus placebo

Outcome: 1 Clinical relapse

Study or subgroup	Sulfasalazine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wenckert 1978	6/32	11/34		100.0 %	0.58 [0.24, 1.38]
Total (95% CI)	**32**	**34**		**100.0 %**	**0.58 [0.24, 1.38]**
Total events: 6 (Sulfasalazine), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Not applicable					

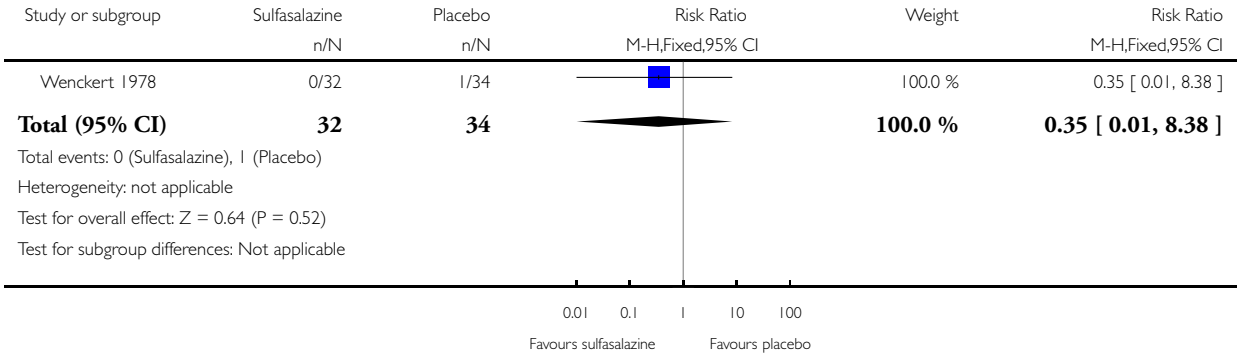


Analysis 11.2. Comparison 11 Direct evidence: sulfasalazine versus placebo, Outcome 2 Adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 11 Direct evidence: sulfasalazine versus placebo

Outcome: 2 Adverse events

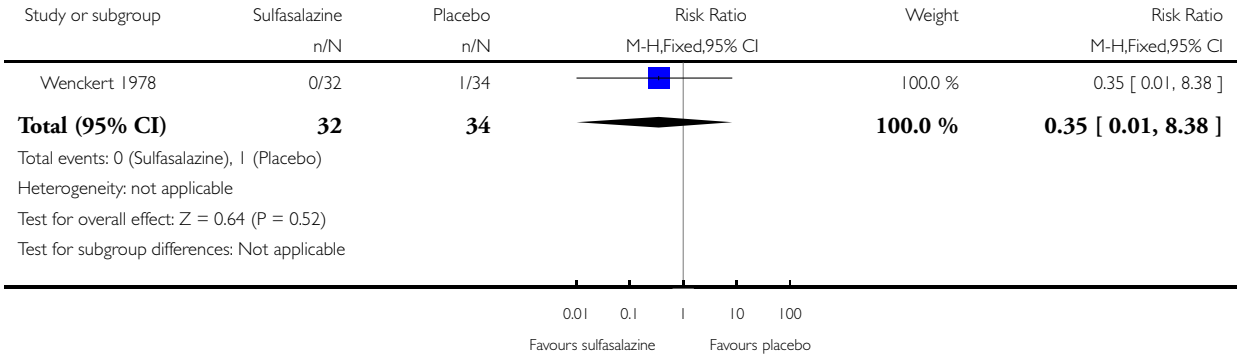


Analysis 11.3. Comparison 11 Direct evidence: sulfasalazine versus placebo, Outcome 3 Withdrawal due to adverse events.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 11 Direct evidence: sulfasalazine versus placebo

Outcome: 3 Withdrawal due to adverse events

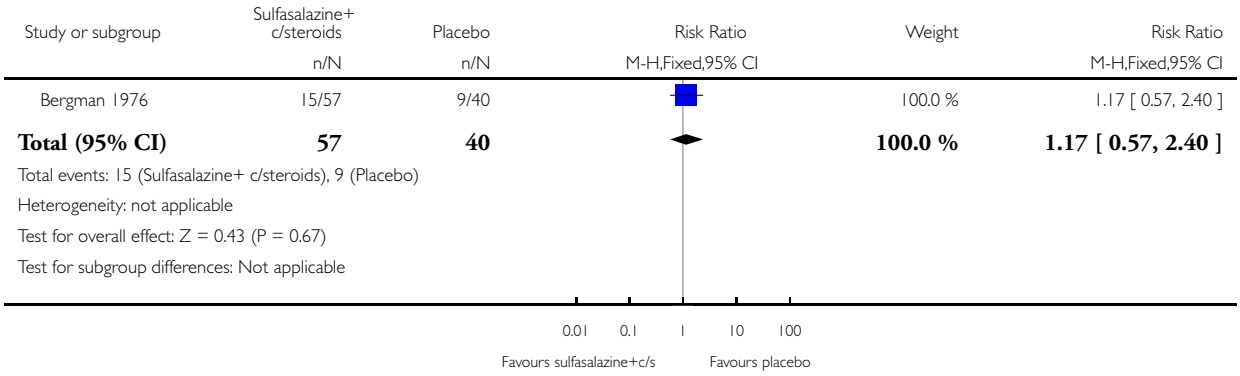


Analysis 12.1. Comparison 12 Direct evidence: sulfasalazine + prednisolone versus placebo, Outcome 1 Clinical relapse.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 12 Direct evidence: sulfasalazine + prednisolone versus placebo

Outcome: 1 Clinical relapse

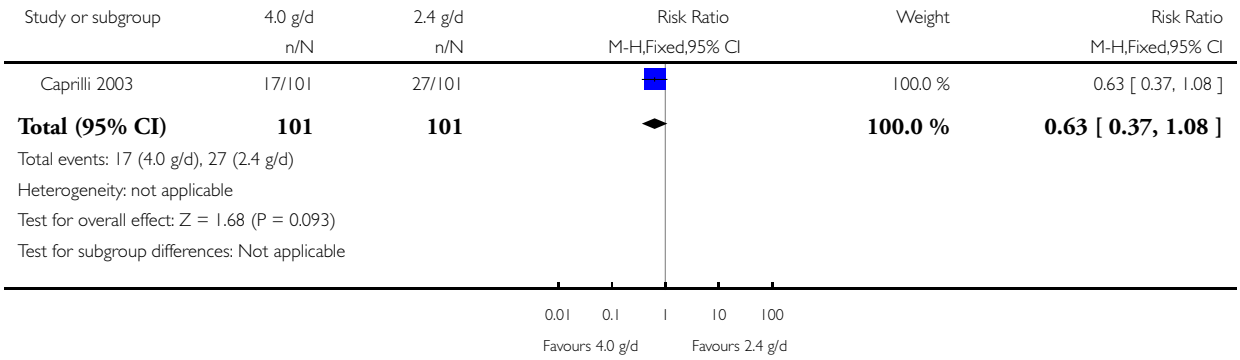


Analysis 13.1. Comparison 13 Direct evidence not in network: clinical relapse, Outcome 1 4.0 g/d versus 2.4 g/d mesalazine.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 13 Direct evidence not in network: clinical relapse

Outcome: 1 4.0 g/d versus 2.4 g/d mesalazine

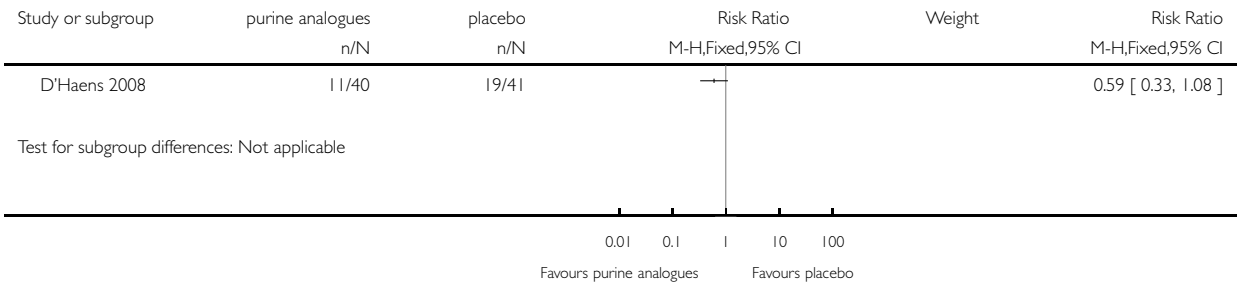


Analysis 13.2. Comparison 13 Direct evidence not in network: clinical relapse, Outcome 2 Purine analogues versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 13 Direct evidence not in network: clinical relapse

Outcome: 2 Purine analogues versus placebo

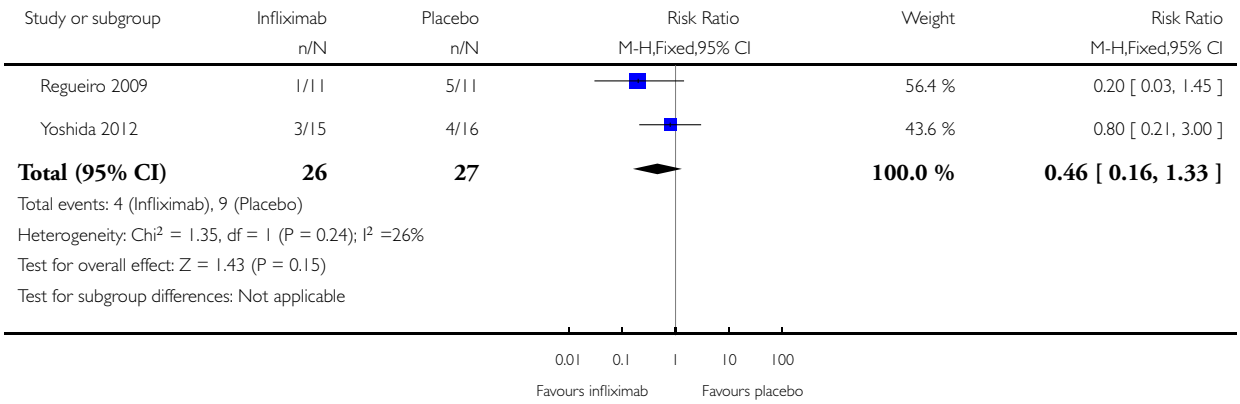


Analysis 13.3. Comparison 13 Direct evidence not in network: clinical relapse, Outcome 3 Infliximab versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 13 Direct evidence not in network: clinical relapse

Outcome: 3 Infliximab versus placebo

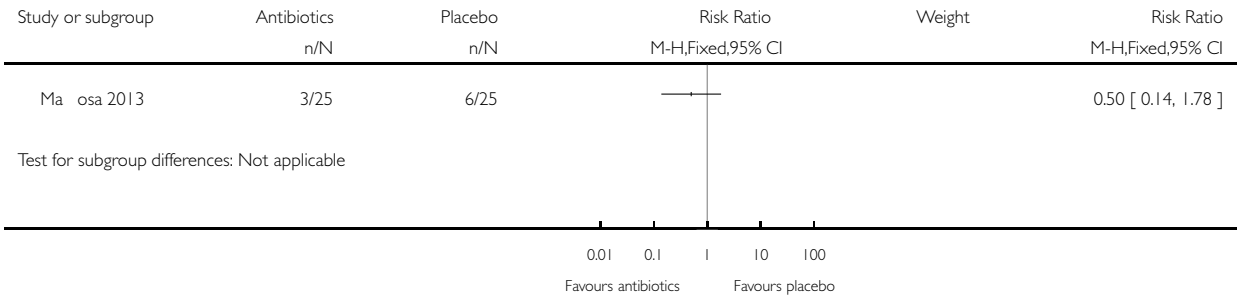


Analysis 13.4. Comparison 13 Direct evidence not in network: clinical relapse, Outcome 4 Antibiotics versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 13 Direct evidence not in network: clinical relapse

Outcome: 4 Antibiotics versus placebo



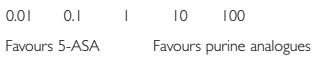
Analysis 13.5. Comparison 13 Direct evidence not in network: clinical relapse, Outcome 5 5-ASA versus purine analogues.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 13 Direct evidence not in network: clinical relapse

Outcome: 5 5-ASA versus purine analogues

Study or subgroup	5-ASA n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Reinisch 2010	25/41	22/37		100.0 %	1.03 [0.71, 1.47]
Total (95% CI)	**41**	**37**		**100.0 %**	**1.03 [0.71, 1.47]**
Total events: 25 (5-ASA), 22 (Purine analogues)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
Test for subgroup differences: Not applicable					



Analysis 14.1. Comparison 14 Direct evidence not in network: adverse events, Outcome 1 4.0 g/d versus 2.4 g/d mesalazine.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 14 Direct evidence not in network: adverse events

Outcome: 1 4.0 g/d versus 2.4 g/d mesalazine

Study or subgroup	Favours 4.0 g/d n/N	2.4 g/d n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caprilli 2003	2/101	2/105		100.0 %	1.04 [0.15, 7.24]
Total (95% CI)	**101**	**105**		**100.0 %**	**1.04 [0.15, 7.24]**
Total events: 2 (Favours 4.0 g/d), 2 (2.4 g/d)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
Test for subgroup differences: Not applicable					

Analysis 14.2. Comparison 14 Direct evidence not in network: adverse events, Outcome 2 Probiotics versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 14 Direct evidence not in network: adverse events

Outcome: 2 Probiotics versus placebo

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fedorak 2015	4/58	5/62			0.86 [0.24, 3.03]

Test for subgroup differences: Not applicable

Analysis 14.3. Comparison 14 Direct evidence not in network: adverse events, Outcome 3 Infliximab versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 14 Direct evidence not in network: adverse events

Outcome: 3 Infliximab versus placebo

Study or subgroup	Infliximab n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fukushima 2018	3/21	0/22		0.8 %	7.32 [0.40, 133.66]
Regueiro 2009	8/11	9/11		14.3 %	0.89 [0.56, 1.40]
Regueiro 2016	19/147	54/150		84.9 %	0.36 [0.22, 0.57]
Total (95% CI)	**179**	**183**		**100.0 %**	**0.49 [0.34, 0.70]**

Total events: 30 (Infliximab), 63 (Placebo)

Heterogeneity: Chi^2 = 11.57, df = 2 (P = 0.003); I^2 =83%

Test for overall effect: Z = 3.85 (P = 0.00012)

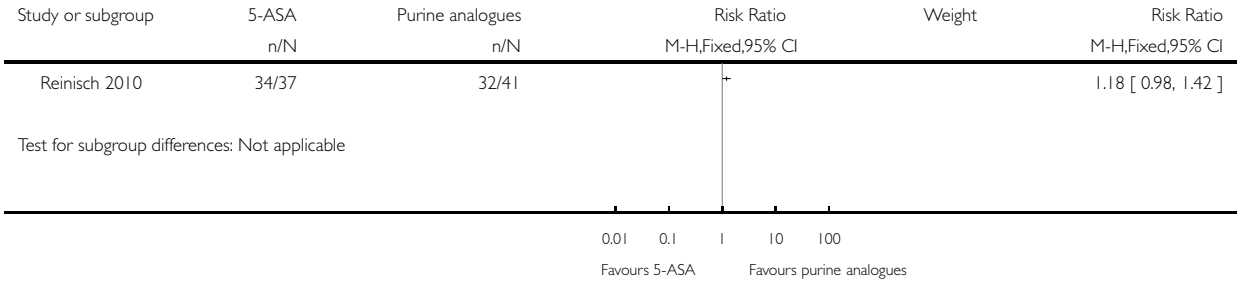
Test for subgroup differences: Not applicable

Analysis 14.4. Comparison 14 Direct evidence not in network: adverse events, Outcome 4 5-ASA versus purine analogues.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 14 Direct evidence not in network: adverse events

Outcome: 4 5-ASA versus purine analogues

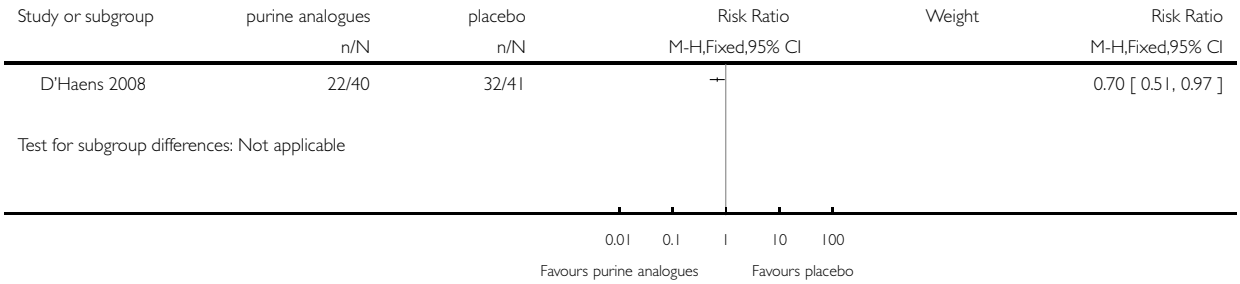


Analysis 14.5. Comparison 14 Direct evidence not in network: adverse events, Outcome 5 Purine analogues versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 14 Direct evidence not in network: adverse events

Outcome: 5 Purine analogues versus placebo

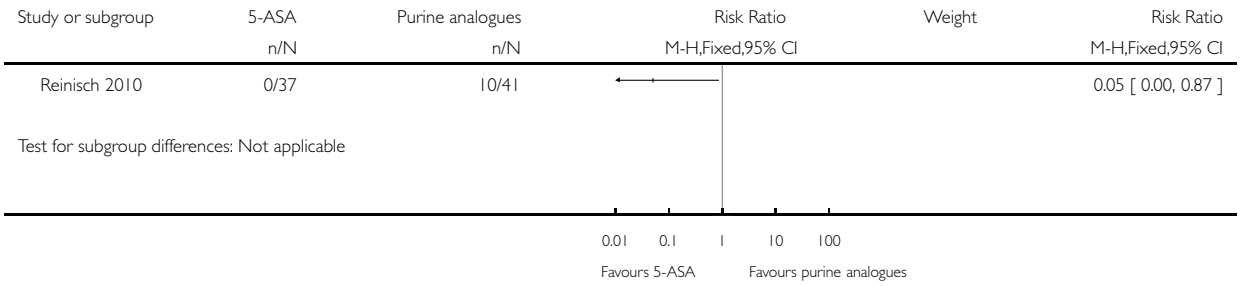


Analysis 15.1. Comparison 15 Direct evidence not in network: serious adverse events, Outcome 1 5-ASA versus purine analogues.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 15 Direct evidence not in network: serious adverse events

Outcome: 1 5-ASA versus purine analogues

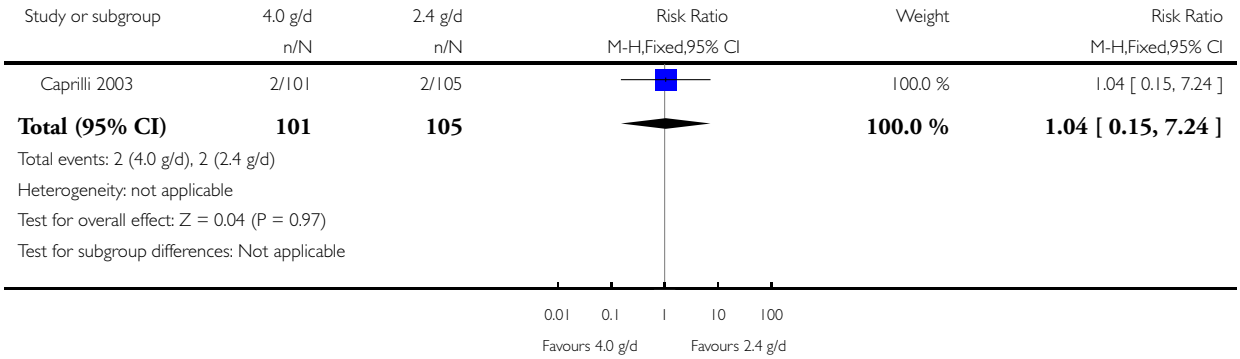


Analysis 16.1. Comparison 16 Direct evidence not in network: withdrawal due to adverse events, Outcome 1 4.0 g/d versus 2.4 g/d mesalazine.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 16 Direct evidence not in network: withdrawal due to adverse events

Outcome: 1 4.0 g/d versus 2.4 g/d mesalazine

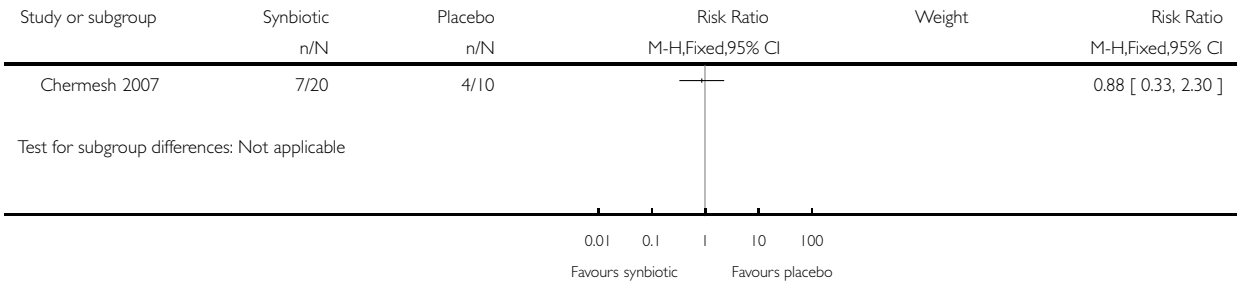


Analysis 16.2. Comparison 16 Direct evidence not in network: withdrawal due to adverse events, Outcome 2 Synbiotic versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 16 Direct evidence not in network: withdrawal due to adverse events

Outcome: 2 Synbiotic versus placebo

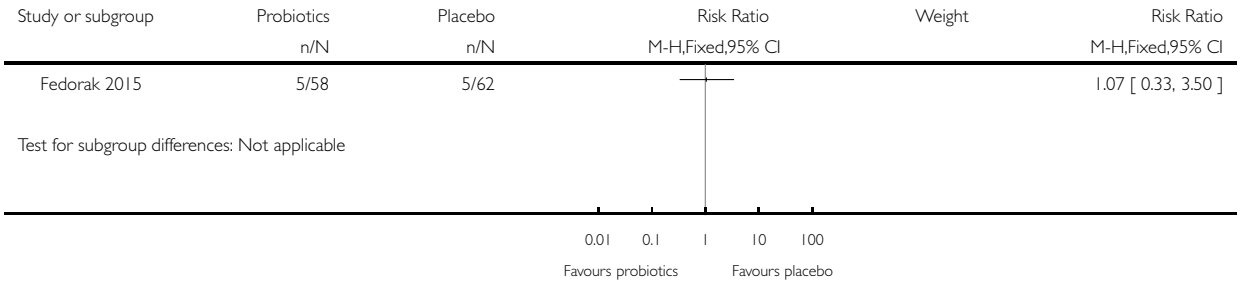


Analysis 16.3. Comparison 16 Direct evidence not in network: withdrawal due to adverse events, Outcome 3 Probiotics versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 16 Direct evidence not in network: withdrawal due to adverse events

Outcome: 3 Probiotics versus placebo



Analysis 16.4. Comparison 16 Direct evidence not in network: withdrawal due to adverse events, Outcome 4 Infliximab versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 16 Direct evidence not in network: withdrawal due to adverse events

Outcome: 4 Infliximab versus placebo

Study or subgroup	Infliximab n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fukushima 2018	3/21	0/22		0.9 %	7.32 [0.40, 133.66]
Regueiro 2009	2/11	1/11		1.8 %	2.00 [0.21, 18.98]
Regueiro 2016	19/147	54/150		96.4 %	0.36 [0.22, 0.57]
Yoshida 2012	1/15	0/16		0.9 %	3.19 [0.14, 72.69]
Total (95% CI)	**194**	**199**		**100.0 %**	**0.47 [0.31, 0.72]**

Total events: 25 (Infliximab), 55 (Placebo)

Heterogeneity: $Chi^2 = 7.75$, df = 3 (P = 0.05); $I^2 = 61\%$

Test for overall effect: Z = 3.46 (P = 0.00054)

Test for subgroup differences: Not applicable

Analysis 16.5. Comparison 16 Direct evidence not in network: withdrawal due to adverse events, Outcome 5 5-ASA versus purine analogues.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 16 Direct evidence not in network: withdrawal due to adverse events

Outcome: 5 5-ASA versus purine analogues

Study or subgroup	5-ASA n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Reinisch 2010	1/37	10/41			0.11 [0.01, 0.82]

Test for subgroup differences: Not applicable

Analysis 16.6. Comparison 16 Direct evidence not in network: withdrawal due to adverse events, Outcome 6 Purine analogues versus placebo.

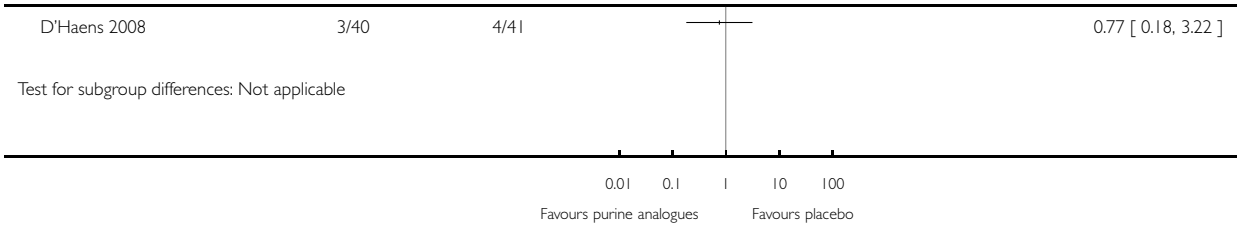
Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 16 Direct evidence not in network: withdrawal due to adverse events

Outcome: 6 Purine analogues versus placebo

Study or subgroup	purine analogues n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
D'Haens 2008	3/40	4/41			0.77 [0.18, 3.22]

Test for subgroup differences: Not applicable



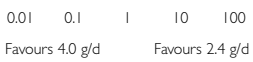
Analysis 17.1. Comparison 17 Direct evidence not in network: endoscopic relapse, Outcome 1 4.0 g/d versus 2.4 g/d mesalazine.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 17 Direct evidence not in network: endoscopic relapse

Outcome: 1 4.0 g/d versus 2.4 g/d mesalazine

Study or subgroup	4.0 g/d n/N	2.4 g/d n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Caprilli 2003	45/101	59/105		100.0 %	0.79 [0.60, 1.04]
Total (95% CI)	**101**	**105**		**100.0 %**	**0.79 [0.60, 1.04]**
Total events: 45 (4.0 g/d), 59 (2.4 g/d)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.099)					
Test for subgroup differences: Not applicable					



Analysis 17.2. Comparison 17 Direct evidence not in network: endoscopic relapse, Outcome 2 Probiotics versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 17 Direct evidence not in network: endoscopic relapse

Outcome: 2 Probiotics versus placebo

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fedorak 2015	47/58	50/62			1.00 [0.84, 1.20]
Test for subgroup differences: Not applicable					

Analysis 17.3. Comparison 17 Direct evidence not in network: endoscopic relapse, Outcome 3 Infliximab versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 17 Direct evidence not in network: endoscopic relapse

Outcome: 3 Infliximab versus placebo

Study or subgroup	Infliximab n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fukushima 2018	12/21	16/22		11.3 %	0.79 [0.50, 1.23]
Regueiro 2009	1/11	11/13		7.3 %	0.11 [0.02, 0.71]
Regueiro 2016 (1)	67/147	101/150		72.3 %	0.68 [0.55, 0.83]
Yoshida 2012	4/15	13/16		9.1 %	0.33 [0.14, 0.78]
Total (95% CI)	**194**	**201**		**100.0 %**	**0.62 [0.51, 0.74]**

Total events: 84 (Infliximab), 141 (Placebo)

Heterogeneity: $Chi^2 = 7.21$, df = 3 (P = 0.07); $I^2 = 58\%$

Test for overall effect: Z = 5.08 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Endoscopic score

Analysis 17.4. Comparison 17 Direct evidence not in network: endoscopic relapse, Outcome 4 5-ASA versus purine analogues.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 17 Direct evidence not in network: endoscopic relapse

Outcome: 4 5-ASA versus purine analogues

Study or subgroup	5-ASA n/N	Purine analogues n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Reinisch 2010	1/37	10/41			0.11 [0.01, 0.82]

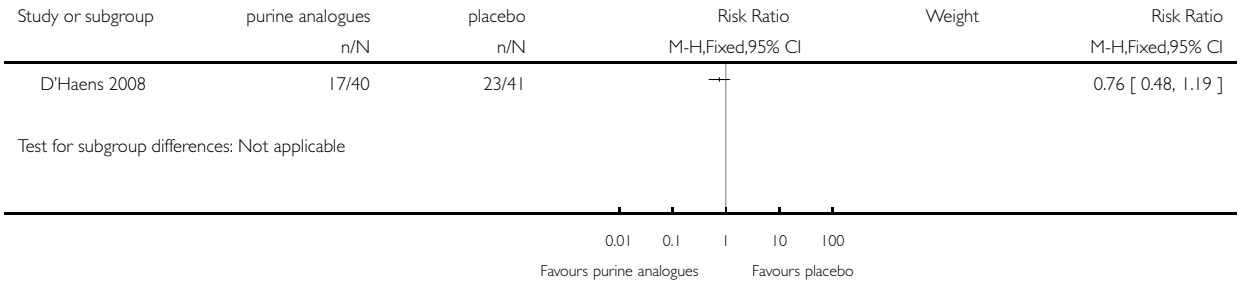
Test for subgroup differences: Not applicable

Analysis 17.5. Comparison 17 Direct evidence not in network: endoscopic relapse, Outcome 5 Purine analogues versus placebo.

Review: Interventions for maintenance of surgically induced remission in Crohn' s disease: a network meta-analysis

Comparison: 17 Direct evidence not in network: endoscopic relapse

Outcome: 5 Purine analogues versus placebo



ADDITIONAL TABLES

Table 1. Summary of interventions and outcome data

Study ID	Group 1	Group 2	Group 3	Relapse	Quailty of life	Adverse events/ serious adverse events
Ardizzone 2004	Azathioprine (2 mg/kg/d)	Mesalazine (3 g/day)	n/a	**Clinical:** 32/71 vs 35/71 **Surgical:** 26/71 vs 21/71	n/a	**AE:** 18/71 vs 27/71 **SAE:** 6/71 vs 15/71 **Withdrawal:** 6/71 vs 15/71
Armuzzi 2013	Azathioprine (2.5 mg/kg/d)	Infliximab (5 mg/kg/d)	n/a	**Clinical:** 2/11 vs 1/11 **Endoscopic:** 5/11 vs 1/11 **Histologic:** 9/11	n/a	**Withdrawal:** 0/11 vs 1/11

Table 1. Summary of interventions and outcome data (*Continued*)

				vs 2/11		
Bergman 1976	Sulfasalazine (Salazopyrin) + prednisolone	No treatment	n/a	**Relapse:** 15/57 vs 9/40	n/a	Not reported for duration of treatment
Brignola 1995	Mesalazine (3 g/d)	Placebo	n/a	**Clinical:** 13/44 vs 14/43	n/a	**Withdrawal:** 5/44 vs 3/43
Caprilli 1994	Mesalazine (2.4 g/d)	No treatment	n/a	**Relapse:** 20/55 vs 28/55	n/a	**AE:** 2/55 vs 0/55 (all withdrawn)
Caprilli 2003	Mesalazine (4 g/d)	Mesalazine (2.4 g/day)	n/a	**Clinical:** 17/101 vs 27/101 **Endoscopic > 1:** 45/101 vs 59/105	n/a	**AE:** 2/101 vs 2/105 (all withdrawn)
Chermesh 2007	Synbiotic 2000	Placebo	n/a	**Clinical:** n.s. difference in relapse rate **Endoscopic**: n.s. difference in relapse rate	n/a	**Withdrawal:** 7/20 vs 4/10
D'Haens 2008	Metronidazole (750 mg/d) + azathioprine (100 to 150 mg/d)	Metronidazole (750 mg/d) + placebo	n/a	**Clinical:** 11/40 vs 19/41 **Endoscopic:** 22/40 vs 32/41	n/a	**AE:** 3/40 vs 4/41 **Withdrawal:** 3/40 vs 2/41
Ewe 1989	Sulfasalazine (3 g/d)	Placebo	n/a	**Relapse:** Total 0 to 36 months: 89/111 vs 99/121	n/a	n/a
Ewe 1999	Budesonide (1 mg/d)	Placebo	n/a	**Clinical:** 14/43 vs 19/40 **Histologic:** 36/43 vs 38/43	**QOL:** slight preponderance of medium and good at the end in Group 1	**AE:** 13/43 vs 7/40 **Withdrawal:** 1/40 vs 1/40
Fedorak 2015	VSL#3 twice daily	Placebo	n/a	**Endoscopic:** 47/58 vs 50/62	**IBDQ:** similar between groups (data not shown)	**AE:** 4/58 vs 5/62 **Withdrawal:** 5/58 vs 5/62

Table 1. Summary of interventions and outcome data (*Continued*)

Florent 1996	Mesalazine (Claversal) (1000 mg/d)	Placebo (1000 mg/d)	n/a	**Endoscopic:** 38/65 vs 40/61	n/a	**AE:** 5/65 vs 3/61 (all withdrawn)
Fukushima 2018	Infliximab (5 mg/kg)	No treatment	n/a	**Relapse (endoscopic or clinical or both):** 0 to 24 months: 12/21 vs 21/22 **Clinical:** 0 to 24 months: 9/21 vs 21/22 **Endoscopic:** 0 to 24 months: 12/21 vs 16/22	n/a	**AE:** 3/21 vs 0/22 **Withdrawal:** 3/21 vs 0/22
Gossum 2007	Probiotic *Lactobacillus johnsonii*	Placebo	n/a	**Clinical:** 11/34 vs 17/36 **Endoscopic:** 28/34 vs 27/36 **Histological score:** changes n. s. P = 0.83	n/a	**AE:** Group 1: 65% at least 1 AE, 2% probably related to treatment **SAE:** Group 1: 21% at least 1 SAE (0 related to treatment); Group 2: 22% at least 1 SAE **Withdrawal:** 9 total
Hanauer 2004	6-mercaptopurine (50 mg/d)	Mesalazine (3 g/d)	Placebo	**Clinical:** 32/47 vs 33/44 vs 35/40	n/a	**AE:** 9/47 vs 6/44 vs 4/40 **SAE:** 2/47 vs 0/44 vs 2/40 **Withdrawal:** 9/47 vs 6/44 vs 4/40
Hellers 1999	Budesonide (6 mg/d)	Placebo	n/a	Reported according to the site of inflammation but not mutually exclusive (neoterminal ileum and anastomosis)	n/a	**Adverse:** 44/63 vs 51/67 **Withdrawal:** 5/63 vs 5/67
Herfarth 2006	Azathioprine	5-ASA	n/a	**Clinical:** 23/42 vs 27/37	n/a	**Withdrawal :** 7/42 vs 3/37

Table 1. Summary of interventions and outcome data (*Continued*)

Herfarth 2013	Ciprofloxacin (1000 mg/d)	Placebo	n/a	**Clinical:** 10/17 vs 8/16 **Endoscopic:** 11/17 vs 11/16	n/a	**AE:** 1/17 vs 6/16 **Withdrawal:** 1/17 vs 4/16
Lochs 2000	Mesalazine (4 g/d)	Placebo	n/a	**Clinical:** 47/154 vs 59/170 **Endoscopic:** 133/154 vs 134/170	n/a	**SAE:** 8/154 vs 9/170
Lopez Sanroman 2017	Azathioprine (2.5 mg/kg/d) + metronidazole (750 mg/d)	Adalimumab + metronidazole (750 mg/d)	n/a	**Clinical:** 14/39 vs 7/45 **Endoscopic:** 23/39 vs 19/45 **Radiologic:** 26/39 vs 22/45	n.s. changes between groups	**AE:** 20/45 vs 18/39 **SAE:** 9/45 vs 4/39 **Withdrawal:** 1/39 vs 9/45
Mañosa 2013	Metronidazole (15 to 20 mg/kg/d)	Placebo	n/a	**Clinical:** not reported at 3 months **Severe endoscopic (i $\geq$ 3):** not reported at 3 months	n/a	**AE:** 7/25 vs 12/25 **SAE:** 1/25 vs 4/25 **Withdrawal:** 4/25 vs 1/25
Marteau 2006	*Lactobacillus johnsonii* LA1 (2 packs/d)	Placebo	n/a	**Clinical:** 9/48 vs 6/50 **Endoscopic:** 26/48 vs 33/50	n/a	**AE:** 9/48 vs 6/50 **Withdrawal:** 0
McLeod 1995	Mesalazine (3 g/d)	Placebo	n/a	**Symptomatic relapse:** 35/88 vs 44/81 **Endoscopic and radiologic rate:** significantly decreased in Group 1	n/a	**AE:** 7/88 vs 10/81 **SAE:** 1/88 vs 0/81
Mowat 2016	Mercaptopurine (1 mg/kg/d)	Placebo	n/a	**Clinical:** 66/128 vs 70/112 **Endoscopic:** 90/128 vs 83/112	n.s. differences	**SAE:** 3/128 vs 2/112 **Withdawal:** 39/128 vs 41/112
Prantera 2002	LGG probiotic (2.46 g/d)	Placebo	n/a	**Clinical:** 8/23 vs 5/22 **Endoscopic:** 17/23 vs 11/22	n/a	**AE:** 2/23 vs 6/22 **Withdrawal:** 0

Table 1. Summary of interventions and outcome data (*Continued*)

Regueiro 2009	Infliximab	Placebo	n/a	**Clinical:** 1/11 vs 5/11 **Endoscopic:** 1/11 vs 11/13	n/a	**AE:** 8/11 vs 9/11 **Withdrawal:** 2/11 vs 1/11
Regueiro 2016	Infliximab (5 mg/kg)	Placebo	n/a	**Endoscopic by ileocolonoscopy:** 90/147 vs 130/150 **Endoscopic by endoscopic score only:** 67/147 vs 101/150	n/a	**AE:** 19/147 vs 54/150 **Withdrawal:** 19/147 vs 54/150
Reinisch 2010	Azathioprine (2.0 to 2.5 mg/kg/d) + placebo mesalazine	Mesalazine (4 g/d) + placebo azathioprine	n/a	Not included	**Mean IBDQ change** P = n.s.	**AE:** 34/37 vs 32/41 **SAE:** 0/37 vs 10/41 **Withdrawal:** 1/37 vs 10/41
Rutgeerts 2005	Ornidazole (1000 mg/d)	Placebo	n/a	**Clinical:** 17/40 vs 20/40 **Endoscopic:** 27/40 vs 33/40 **Radiologic:** 24/40 vs 33/40	n/a	Not reported
Savarino 2013	Adalimumab (160 to 80 mg 0 to 2 weeks and 40 mg thereafter)	Azathioprine (2 mg/kg/d)	Mesalazine (3g/d)	**Clinical by Hanauer score:** 2/16 vs 12/17 vs 9/18 **Clinical by CDAI:** 1/16 vs 12/17 vs 9/18 **Endoscopic:** 1/16 vs 11/17 vs 15/18 **Radiologic:** 1/16 vs 13/17 vs 15/18	**HRQOL (IBDQ > 170):** 14/16 vs 2/17 vs 3/18	**AE:** 11/16 vs 14/17 vs 14/18 **Withdrawal:** 0/16 vs 1/17 vs 1/18
Scapa 2015	6-mercaptopurine (1.5 mg/kg/d)	Adalimumab (160-80-40 mg/2-week intervals)	n/a	**Endoscopic:** 4/8 vs 1/11	n/a	n/a

Table 1. Summary of interventions and outcome data (*Continued*)

Sutherland 1997	Mesalazine (3 g/d)	Placebo	n/a	**Clinical:** 3/31 vs 8/35	**IBDQ score:** significant decline in both groups	n/a
Tursi 2014	Infliximab (5 mg/kg) at 0, 2, and thereafter 8-week intervals	Adalimumab (160-80-40 mg/2-week intervals)	n/a	**Clinical:** 1/10 vs 1/10 **Endoscopic:** 2/10 vs 1/10 **Histologic:** 3/10 vs 2/10	n/a	**AE:** 0/10 vs 0/10
Wenckert 1978	Sulfasalazine (3 g/d)	Placebo	n/a	**Clinical:** 6/32 vs 11/34	n/a	**AE:** 0/32 vs 1/34 (withdrawn)
Yoshida 2012	Infliximab (5 mg/kg at 8-week intervals)	Participant's conventional medication started longer than 8 weeks prior to surgery	n/a	**Clinical (CDAI):** 3/15 vs 4/16 **Clinical (IOIBD score):** 1/15 vs 7/16 **Endoscopic:** 4/15 vs 13/16 **Serologic:** 2/15 vs 10/16	n/a	**Withdrawal:** 1/15 vs 0/16

5-ASA: 5-aminosalicylic acid; AE: adverse events; CDAI: Crohn's disease activity index; HRQOL: health-related quality of life; IBDQ: inflammatory bowel disease questionnaire; IOIBD: International Organization for the Study of Inflammatory Bowel Diseases; n/a: not applicable; n.s.:not significant; QOL: quality of life; SAE: serious adverse events

Table 2. Summary of key study characteristics and outcome definition

Comparison	Study	Time from surgery until recruitment	Site of surgery % / *exclusions	Clinical relapse definition	Endoscopic/ histological relapse definition/other
Sulfasalazine vs placebo					
SFZ 3 g/d vs placebo	Ewe 1989	Immediately after surgery	Ileocolon 92; Ileum 2; colon 6 *Non-standard policy resection (radical or non-radical)	Proven by radiology, endoscopy, or operation	n/a
SFZ 3 g/d vs placebo	Wenckert 1978	2 to 4 weeks	n/a	Special control charts	n/a

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

5-ASA vs no treatment/placebo					
MEZ 2.4 g/d (24 months) vs no treatment	Caprilli 1994	2 weeks	Not reported *Disease localisation to the jejunum, proximal ileum, left colon, or ano-rectum	CDAI > 150	n/a
MEZ 3 g/d vs placebo 3 g (12 months)	Brignola 1995	≤ 1 months	Ileum 56, ileocaecal 46 *Surgery other than in ileal or ileocaecal region	CDAI > 150	Standardised form for description of endoscopic lesions by type and characteristics
MEZ 1.5 g/d vs placebo (12 weeks)	Florent 1996	2 weeks	Ileal 44; colonic 6; ileocolonic 48; anoperineal lesion 12 *Permanent stoma, small intestinal resection of more than 100 cm prior to the pretrial operation	n/a	Rutgeerts i ≥ 1
MEZ 3 g/d vs placebo (24 months)	Hanauer 2004	Before postoperative hospital discharge	Not reported *Active perianal disease or any active disease in other segments of the intestine	Clinical recurrence grading > 2	Rutgeerts i ≥ 2 **Radiographic relapse:** radiographic recurrence grading > 2
MEZ 4 g/d vs placebo (18 months)	Lochs 2000	< 10 days	Ileal 49; ileocolonic 56; colonic 5 *Short bowel syndrome, presence of an ileocolonic stoma, more than 3 surgeries	CDAI > 250 and CDAI > 200 but minimum 60 points increase for 2 weeks	Rutgeerts i ≥ 2
Ileum 50, MEZ 3 g/d vs placebo	McLeod 1995	≤ 8 weeks	Ileal 21; ileocolonic 46; colonic 33	Severe symptoms to warrant treatment and radiological or endoscopic evidence of disease	Presence of endoscopic or radiological evidence of disease and included both asymptomatic and symptomatic patients

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

MEZ 3 g/d vs placebo	Sutherland 1997	2 to 4 weeks	Ileal 49, ileocolonic 50, unknown 1	CDAI > 150 as well as the absolute value of at least 60 points higher than baseline	n/a
5-ASA vs purine analogues					
MEZ 3 mg/kg vs AZA 2 mg/kg	Ardizzone 2004	Max 2 weeks	Small bowel only 25. 3; colon 5.6; small bowel and colon 9. 8; upper gastrointestinal tract 16.2 *Surgical procedures other than conservative surgery or for perianal disease only	CDAI > 200	n/a **Surgical relapse:** need for another surgical procedure
MEZ 3 g/d vs 6-MP 50 mg/d	Hanauer 2004	Before postoperative hospital discharge	Not reported *Active perianal disease or any active disease in other segments of the intestine	Clinical recurrence grading > 2 (Hanauer and colleagues)	Rutgeerts i ≥ 2 **Radiographic relapse:** radiographic recurrence grading > 2
AZA 2.0 to 2.5 mg/kg body weight/day vs 5-ASA 4 g/day	Herfarth 2006	2 weeks	Not reported	Described as treatment failure due to adverse events, serious endoscopic relapse, and lack of efficacy	
MEZ 4 g/d vs AZA 2 mg/kg/d (52 weeks)	Reinisch 2010	6 to 24 months	Not reported *Short bowel syndrome, an ileocolonic stoma	CDAI > 200	Rutgeerts i ≥ 2 **HRQOL: IBDQ**
MEZ 3 g/d vs AZA 2 mg/kg/d	Savarino 2013	2 to 4 weeks	Ileum 49, Ileocolonic 51 *Fibrostenotic stricture, macroscopically active disease not resected at the time of surgery, and presence of a stoma	1. ≥ 2 clinical recurrence grading scale (Hanauer and colleagues) 2. CDAI > 200	Rutgeerts i ≥ 2 **Radiologic relapse**: ≥ 2 radiographic recurrence grading scale **HRQOL:** IBDQ > 170
5-ASA vs adalimumab					

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

MEZ 3 g/d vs adalimumab	Savarino 2013	2 to 4 weeks	Ileum 49, Ileocolonic 51 *Fibrostenotic stricture, macroscopically active disease not resected at the time of surgery, and presence of a stoma	1. ≥ 2 on the clinical recurrence grading scale by Hanauer 2. CDAI > 200	Rutgeerts i ≥ 2 **Radiologic relapse**: ≥ 2 radiographic recurrence grading scale **HRQOL:** IBDQ > 170
5-ASA vs 5-ASA					
4.0 g/d MEZ vs 2.4 g/d MEZ (12 months)	Caprilli 2003	2 weeks	Ileum 64; Ileum/caecum/ascending colon 36 *Disease localisation to jejunum, proximal ileum, transverse colon, left colon or anorectum	CDAI > 150 points or an increase in CDAI score of + 100 points from baseline	Rutgeerts i ≥ 1
Purine analogues vs placebo					
AZA 100 to 150 mg/d + metronidazole 750 mg/d vs placebo + metronidazole 750 mg/d (12 months)	D'Haens 2008	2 weeks	Perforating disease 48 *Macroscopic evidence for CD proximally or distally to the site of resection or the presence of frank pancolitis or an ileorectal anastomosis, participants with a stoma; operation for fibrostenosis only	CDAI > 250	Rutgeerts i ≥ 2
6-MP 50 mg/d vs placebo	Hanauer 2004	Before postoperative hospital discharge	Not reported *Active perianal disease or any active disease in other segments of the intestine	Clinical recurrence grading > 2 (Hanauer)	Rutgeerts i ≥ 2 **Radiographic relapse:** radiographic recurrence grading > 2
6-MP 1 mg/kg/d vs placebo	Mowat 2016	≤ 3 months	Ileal 39; colonic 2; ileocolonic 59 *Need for further surgery, strictureplasty alone, formation of a stoma	CDAI > 150 and a 100-point increase from baseline	Rutgeerts i ≥ 2 **HRQOL:** IBDQ scores

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

Purine analogues vs 5-ASA					
AZA 2 mg/kg vs MEZ 3 mg/kg	Ardizzone 2004	Max 2 weeks	Small bowel only 25. 3; colon 5.6; small bowel and colon 9. 8; upper gastrointestinal tract 16.2 *Surgical procedures other than conservative surgery or for perianal disease only	CDAI > 200	n/a **Surgical relapse:** need for another surgical procedure
6-MP 50 mg/d vs MEZ 3 g/d	Hanauer 2004	Before postoperative hospital discharge	Not reported *Active perianal disease or any active disease in other segments of the intestine	Clinical recurrence grading > 2	Rutgeerts i ≥ 2 **Radiographic relapse:** radiographic recurrence grading > 2
AZA 2 mg/kg/d vs MEZ 4 g/d (52 weeks)	Reinisch 2010	6 to 24 months	Not reported *Short bowel syndrome and ileocolonic stoma	CDAI > 200	Rutgeerts i ≥ 2 **HRQOL: IBDQ**
AZA 2 mg/kg/d vs MEZ 3 g/d	Savarino 2013	2 to 4 weeks	Ileum 49, ileocolonic 51 *Fibrostenotic stricture, macroscopically active disease not resected at the time of surgery, and presence of a stoma	1. ≥ 2 on the clinical recurrence grading scale by Hanauer 2. CDAI > 200	Rutgeerts i ≥ 2 **Radiologic relapse**: ≥ 2 radiographic recurrence grading scale **HRQOL:** IBDQ > 170
Purine analogues vs adalimumab					
AZA 2.5 mg vs INF 5 mg/kg	Armuzzi 2013	2 to 4 weeks	Not reported *Active perianal disease, presence of stoma	HBI ≥ 8	Rutgeerts' score ≥ i2
AZA 2 mg/kg/d vs adalimumab	Savarino 2013	2 to 4 weeks	Ileum 49, ileocolonic 51 *Fibrostenotic stricture, macroscopically active disease not resected at the time of surgery, and	1. ≥ 2 on the clinical recurrence grading scale by Hanauer 2. CDAI > 200	Rutgeerts i ≥ 2 **Radiologic relapse**: ≥ 2 radiographic recurrence grading scale **HRQOL:** IBDQ >

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

			presence of a stoma		170
AZA 2.5 mg/kg/d vs adalimumab (12 months)	Lopez Sanroman 2017	2 weeks	Ileal 58, ileocolonic 41 *Postsurgical stoma, resec- tion for short indolent stenosis, inaccessible anastomosis to endoscopy	CDAI > 200	Rutgeerts i ≥ 2
6-MP 1.5 mg/kg/d vs adalimumab (12 months)	Scapa 2015	< 45 days	Not reported *Not reported	n/a	Rutgeerts i ≥ 2
Functional foods vs placebo					
Synbiotic 2000 vs placebo (24 months)	Chermesh 2007	As soon as participants resume oral intake after surgery	Not reported *Not reported	CDAI, definition not stated (presented as mean change)	Rutgeerts score, definition not stated (presented as mean change)
VSL#3, 2 sachets/d vs placebo 3 g/d	Fedorak 2015	< 30 days	Not reported *Residual luminal disease; participants receiving anti-TNF	Not reported	Rutgeerts score ≥ 1 **HRQOL: IBDQ**
Probiotic LA1, 2 g/d vs placebo (3 months)	Gossum 2007	< 7 days	Ileum only 9; colon only 4; ileo-colonic 87 *Active perianal disease or any active disease in other segments of the intestine; bowel surgery performed less than 3 months previously; history of colostomy or ileostomy	CDAI > 150, and increase of minimum 70 points from baseline	Rutgeerts score ≥ 1
Probiotic LA1, 2 sachets/d vs placebo (6 months)	Marteau 2006	< 21 days	Ileum 55; ileocolon 41; colon 4 *Total or subtotal colectomy, intestinal bypass or stricturoplasty, stomy, carcinoma resection, or abscess	CDAI ≥ 200	Rutgeerts i ≥ 2

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

			drainage		
Probiotic LGG, 5 g/d vs placebo (12 months)	Prantera 2002	< 10 days	Ileum 78; ileocolon 13; colon 9 *Active perianal disease; presence of CD in other intestinal tracts; postoperative septic complications	CDAI > 150	Rutgeerts i ≥ 2
Budesonide vs placebo					
Budesonide 3 mg/d vs placebo (12 months)	Ewe 1999	< 2 weeks	Ileum 25, colon 15, ileocolon 60 *Not reported	CDAI > 200, rise for 60 points	Rutgeerts i ≥ 2
Budesonide 6 mg/d vs placebo (12 months)	Hellers 1999	< 2 weeks	Not reported *Septic complications, > 100 cm of terminal ileum resected	CDAI score presented is mean change.	Rutgeerts i ≥ 2
Antibiotics vs placebo					
Ciprofloxacin 1 g/d vs placebo (6 months)	Herfarth 2013	< 2 weeks	Non-stricturing, non-penetrating 18; stricturing 55; penetrating 27 *Gross evidence of CD at the operative margins or in the proximal or distal segments of the intestine, presence of a stoma	HBI ≥ 5	Rutgeerts score ≥ i2 or Marteau score ≥ c2
Ornidazole 1 g/d vs placebo (12 months)	Rutgeerts 2005	0 to 1 week	Not reported *Pure fibrostenotic disease without biologic inflammation, stricture-plasties, 2-step resections with temporary ileostoma	CDAI > 250	Rutgeerts score ≥ i2
Metronidazole 20 mg/kg/d + AZA 2 to 2.5 mg/kg/d	Mañosa 2013	As soon as participants resume oral intake after surgery	Ileal 64, colonic 2, ileocolonic 34	HBI > 7	Rutgeerts score ≥ i2

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

vs placebo + AZA 2 to 2.5 mg/kg/d					
Infliximab vs inactive treatment					
IFX 5 mg/kg vs no treatment (24 months)	Fukushima 2018	0 to 4 weeks	Ileum 26; colon 10; ileocolon 54 *More than 3 intestinal resections, presence of a stoma	CDAI > 150	Rutgeerts score ≥ i3
IFX vs placebo (12 months)	Regueiro 2009	0 to 4 weeks	Ileum only 21; ileum and colon 79 *Not reported	CDAI > 200	Rutgeerts score ≥ i2
IFX 5 mg/kg vs placebo (104 weeks)	Regueiro 2016	≤ 45 days	Ileum 98; colon 55.7; proximal small intestine, stomach, and/or oesophagus 4.1; perianal 10.1; extra-intestinal manifestations 12.2 *Surgery more than 10 years after CD diagnosis, stricturing disease involving < 10 cm of bowel	CDAI > 200	Rutgeerts score ≥ i2
Infliximab + 5-ASA vs 5-ASA					
IFX 5 mg/kg + MEZ (36 months) vs MEZ (if any) started > 8 weeks prior to surgery	Yoshida 2012	0 to 4 weeks	Ileum 26, ileocolon 74 *Macroscopically active disease missed during surgery or the presence of abscess	1. CDAI >150 2. IOIBD ≥ 2	Rutgeerts score ≥ i2 **Serologic relapse:** CRP level > 0.3 mg/dL
Infliximab vs adalimumab					
IFX 5 mg/kg vs adalimumab 160 mg (12 months)	Tursi 2014	4 to 6 weeks	Not reported *Active perianal disease, the presence of stoma	HBI ≥ 8	Rutgeerts score ≥ i2
Prednisolone + sulfasalazine vs no treatment					

Table 2. Summary of key study characteristics and outcome definition (*Continued*)

Sulfasalazine (Salazopyrin) + prednisolone vs no treatment (36 months)	Bergman 1976	Not reported	Not reported *Not reported	X-ray Typical roentgenological findings for CD	n/a

5-ASA: 5-aminosalicylic acid; 6-MP: 6-mercaptopurine; AZA: azathioprine; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; HBI: Harvey-Bradshaw Index; HRQOL: health-related quality of life; IBDQ: inflammatory bowel disease questionnaire; IFX: infliximab; IOIBD: International Organization for the Study of Inflammatory Bowel Diseases; MEZ: mesalazine; n/a: not applicable; SFZ: sulfasalazine; TNF: tumour necrosis factor

Table 3. Studies included in the network meta-analysis

Included studies	Considered for inclusion in network	Studies in network with clinical relapse data	Studies in network with endoscopic relapse data	Studies in network with safety data
Ardizzone 2004	Ardizzone 2004	Ardizzone 2004	Armuzzi 2013	Ardizzone 2004
Armuzzi 2013	Armuzzi 2013	Armuzzi 2013	Florent 1996	Armuzzi 2013
Bergman 1976	Bergman 1976	Bergman 1976	Gossum 2007	Brignola 1995
Brignola 1995	Brignola 1995	Brignola 1995	Hanauer 2004	Caprilli 1994
Caprilli 1994	Caprilli 1994	Caprilli 1994	Hellers 1999	Ewe 1999
Caprilli 2003[a]	Ewe 1989	Ewe 1989	Herfarth 2013	Fedorak 2015
Chermesh 2007[b]	Ewe 1999	Ewe 1999	Marteau 2006	Florent 1996
D'Haens 2008[b]	Fedorak 2015	Gossum 2007	Mowat 2016	Hanauer 2004
Ewe 1989	Florent 1996	Hanauer 2004	Rutgeerts 2005	Hellers 1999
Ewe 1999	Gossum 2007	Herfarth 2006	Savarino 2013	Herfarth 2006
Fedorak 2015	Hanauer 2004	Herfarth 2013	Scapa 2015	Herfarth 2013
Florent 1996	Hellers 1999	Lochs 2000	Tursi 2014	Mowat 2016
Fukushima 2018[b]	Herfarth 2006	Marteau 2006	Wenckert 1978	Reinisch 2010
Gossum 2007	Herfarth 2013	McLeod 1995		Savarino 2013
Hanauer 2004	Lochs 2000	Mowat 2016		Sutherland 1997

Table 3. Studies included in the network meta-analysis (*Continued*)

Hellers 1999	Marteau 2006	Prantera 2002		Wenckert 1978
Herfarth 2006	McLeod 1995	Rutgeerts 2005		
Herfarth 2013	Mowat 2016	Savarino 2013		
Lochs 2000	Prantera 2002	Sutherland 1997		
Lopez-Sanroman 2017[b]	Reinisch 2010[c]	Tursi 2014		
Marteau 2006	Rutgeerts 2005	Wenckert 1978		
Mañosa 2013[b]	Savarino 2013			
McLeod 1995	Scapa 2015			
Mowat 2016	Sutherland 1997			
Prantera 2002	Tursi 2014			
Regueiro 2009[b]	Wenckert 1978			
Regueiro 2016[b]				
Reinisch 2010				
Rutgeerts 2005				
Savarino 2013				
Scapa 2015				
Sutherland 1997				
Tursi 2014				
Wenckert 1978				
Yoshida 2012[b]				

[a] Randomised participants to receive active treatments that they were receiving prior to randomisation.
[b] Compared two different doses of mesalazine.
[c] Potentially includes people who were not in clinical relapse, therefore only data for withdrawal due to adverse events included, whilst relapse data ignored.

Table 4. Number of participants who experienced clinical relapse

	Study ID	Treatment 1	Events	N	Treatment 2	Events	N	Treatment 3	Events	N
1	Ardizzone 2004	5-ASA	32	71	Purine analogues	35	71	NA	NA	NA
2	Armuzzi 2013	Infliximab	1	11	Purine analogues	2	11	NA	NA	NA
3	Bergman 1976	Placebo	9	40	Sulfasalazine + prednisolone	15	57	NA	NA	NA
4	Brignola 1995	Placebo	14	43	5-ASA	13	44	NA	NA	NA
5	Caprilli 1994	Placebo	28	55	5-ASA	20	55	NA	NA	NA
6	Ewe 1989	Placebo	99	121	Sulfasalazine	89	111	NA	NA	NA
7	Ewe 1999	Placebo	19	40	Budesonide	14	43	NA	NA	NA
8	Gossum 2017	Placebo	17	36	Probiotics	11	34	NA	NA	NA
9	Hanauer 2004	Placebo	35	40	5-ASA	33	44	Purine analogues	32	47
10	Herfarth 2006	5-ASA	27	37	Purine analogues	33	42	NA	NA	NA
11	Herfarth 2013	Placebo	8	16	Antibiotics	10	17	NA	NA	NA
12	Lochs 2000	Placebo	59	170	5-ASA	47	154	NA	NA	NA
13	Marteau 2006	Placebo	6	50	Probiotics	10	48	NA	NA	NA
14	McLeod 1995	Placebo	44	81	5-ASA	35	88	NA	NA	NA
15	Mowat 2016	Placebo	70	112	Purine analogues	66	128	NA	NA	NA

Table 4. Number of participants who experienced clinical relapse (*Continued*)

16	Prantera 2002	Placebo	5	22	Probiotics	8	23	NA	NA	NA
17	Rutgeerts 2005	Placebo	20	40	Antibiotics	17	40	NA	NA	NA
18	Savarino 2013	5-ASA	9	18	Adalimumab	2	16	Purine analogues	13	17
19	Sutherland 1997	Placebo	8	35	5-ASA	3	31	NA	NA	NA
20	Tursi 2014	Adalimumab	1	10	Infliximab	1	10	NA	NA	NA
21	Wenckert 1978	Placebo	11	34	Sulfasalazine	6	32	NA	NA	NA

5-ASA: 5-aminosalicylic acid; N: total number of participants; NA: not applicable

Table 5. Number of participants who experienced endoscopic relapse

	Study ID	Treatment 1	Events	N	Treatment 2	Events	N	Treatment 3	Events	N
1	Armuzzi 2013	Infliximab	1	11	Purine analogues	1	11	NA	NA	NA
2	Florent	Placebo	40	61	5-ASA	38	65	NA	NA	NA
3	Gossum 2007	Placebo	27	36	Probiotics	28	34	NA	NA	NA
4	Herfarth 2013	Placebo	11	16	Antibiotics	11	17	NA	NA	NA
5	Lochs	Placebo	134	170	5-ASA	133	154	NA	NA	NA
6	Marteau 2006	Placebo	33	50	Probiotics	26	48	NA	NA	NA
7	Mowat 2016	Placebo	83	112	Purine analogues	90	128	NA	NA	NA
8	Prantera	Placebo	11	22	Probiotics	17	23	NA	NA	NA
9	Rutgeerts 2005	Placebo	33	40	Antibiotics	27	40	NA	NA	NA

Table 5. Number of participants who experienced endoscopic relapse (*Continued*)

10	Savarino 2013	5-ASA	15	18	Adalimumab	1	16	Purine analogues	11	17
11	Scapa 2015	Adalimumab	1	11	Purine analogues	4	8	NA	NA	NA
12	Tursi 2014	Adalimumab	2	10	Infliximab	1	10	NA	NA	NA

5-ASA: 5-aminosalicylic acid; N: total number of participants; NA: not applicable

Table 6. Number of withdrawals due to adverse events

	Study ID	Treatment 1	Events	N	Treatment 2	Events	N	Treatment 3	Events	N
1	Ardizzone 2004	5-ASA	6	71	Purine analogues	15	71	NA	NA	NA
2	Armuzzi 2013	Infliximab	0	11	Purine analogues	1	11	NA	NA	NA
3	Brignola 1995	Placebo	3	43	5-ASA	5	44	NA	NA	NA
4	Caprilli 1994	Placebo	0	55	5-ASA	2	55	NA	NA	NA
5	Ewe 1999	Placebo	1	40	Budesonide	1	43	NA	NA	NA
6	Fedorak 2015	Placebo	5	62	Probiotics	5	58	NA	NA	NA
7	Florent 1996	Placebo	3	61	5-ASA	5	65	NA	NA	NA
8	Hanauer 2004	Placebo	4	40	5-ASA	6	44	Purine analogues	9	47
9	Heller 1999	Placebo	5	67	Budesonide	5	63	NA	NA	NA
10	Herfarth 2006	5-ASA	3	37	Azathioprine	7	42	NA	NA	BA
11	Herfarth 2013	Placebo	1	17	Antibiotics	4	16	NA	NA	NA

Table 6. Number of withdrawals due to adverse events (*Continued*)

12	Mowat 2016	Placebo	41	112	Purine analogues	39	128	NA	NA	NA
13	Reinisch 2010	5-ASA	1	37	Purine analogues	10	41	NA	NA	NA
14	Savarino 2013	5-ASA	0	18	Adalimumab	1	16	Purine analogues	1	17
15	Wenckert 1978	Placebo	1	34	Sulfasalazine	0	32	NA	NA	NA

5-ASA: 5-aminosalicylic acid; N: total number of participants; NA: not applicable

Table 7. Clinical relapse: model fit

Treatment	Fixed-effect model			Random-effects model		
	Mean	SD	95% CrI	Mean	SD	95% CrI
5-ASA	0.7	0.07	[0.57, 0.85]	0.69	0.09	[0.53, 0.87]
Adalimumab	0.12	0.08	[0.02, 0.32]	0.11	0.08	[0.02, 0.33]
Antibiotics	0.97	0.27	[0.54, 1.60]	0.98	0.31	[0.50, 1.71]
Budesonide	0.65	0.24	[0.29, 1.22]	0.66	0.28	[0.27, 1.34]
Infliximab	0.33	0.52	[0.02, 1.52]	0.36	0.63	[0.02, 1.74]
Probiotic	1.09	0.30	[0.62, 1.78]	1.11	0.33	[0.62, 1.88]
Purine analogues	0.75	0.09	[0.58, 0.94]	0.75	0.12	[0.55, 1.00]
Sulfasalazine	0.91	0.14	[0.66, 1.22]	0.89	0.19	[0.55, 1.30]
Sulfasalazine + prednisolone	1.35	0.64	[0.53, 2.93]	1.37	0.7	[0.50, 3.07]
Between-study heterogeneity	-	-	-	0.13	0.11	[0.01, 0.40]
Total residual deviance[a]	42.91	7.89	[29.45, 60.17]	42.21	8.223	[27.98, 60.07]
DIC[b]	242.60			244.26		

Table 7. Clinical relapse: model fit (*Continued*)

pD	29.58	31.95

Hazard ratios (mean and SD) with credible intervals (Crl); 5-ASA: 5-aminosalicylic acid; DIC: deviance information criterion; pD: number of parameters; SD: standard deviation

[a] Compared to 45 data points.

[b] Difference in DIC (1.65 points) is not significant.

Table 8. Endoscopic relapse: model fit

Treatment	Fixed-effect model			Random-effects model		
	Mean	SD	95% CrI	Mean	SD	95% Crl
5-ASA	1.18	0.14	[0.94, 1.48]	1.22	0.63	[0.61, 2.18]
Adalimumab	0.10	0.06	[0.02, 0.26]	0.10	0.25	[0.01, 0.32]
Antibiotics	0.72	0.18	[0.44, 1.13]	0.80	1.19	[0.33, 1.65]
Infliximab	0.21	0.37	[0.01, 1.02]	0.24	1.75	[0.01, 1.20]
Probiotic	1.09	0.20	[0.76, 1.53]	1.20	0.53	[0.62, 2.19]
Purine analogues	0.87	0.13	[0.64, 1.16]	0.85	0.54	[0.33, 1.61]
Between-study heterogeneity	-	-	-	0.37	0.43	[0.03, 1.58]
Total residual deviance[a]	29.39	6.12	[19.4, 43.22]	26.22	6.77	[14.62, 41.05]
DIC	133.40			133.43		
pD	17.66			20.86		

Hazard ratios (mean and SD) with credible intervals (Crl); 5-ASA: 5-aminosalicylic acid; DIC: deviance information criterion; pD: number of parameters; SD: standard deviation

[a] Compared to 21 data points.

[b] Difference in DIC is not significant (0.03 points).

Table 9. Withdrawals due to adverse event: model fit

Treatment	Fixed-effect model			Random-effects model		
	Mean	SD	95% CrI	Mean	SD	95% CrI
5-ASA	0.699	0.1916	[0.40, 1.14]	1.187	1.103	[0.39, 3.14]
Adalimumab	3.144	10.19	[0.10, 16.04]	11.74	300.8	[0.12, 55.06]
Antibiotics	38.61	679.1	[0.78, 186.70]	53.92	1058	[0.43, 259.80]
Budesonide	1.252	0.8457	[0.32, 3.42]	1.636	11.77	[0.17, 6.19]
Infliximab	1.111	8.673	[3.69E-04, 6.57]	6.374	726.8	[9.14E-04, 21.74]
Probiotics	1.337	1.029	[0.29, 3.98]	2.436	65.24	[0.13, 9.00]
Purine analogues	1.169	0.2339	[0.78, 1.69]	2.512	4.357	[0.79, 7.35]
Sulfasalazine	1.025	7.989	[4.18E-04, 6.052]	1.96	207.6	[3.04E-04, 8.90]
Between-study heterogeneity [a]	-	-	-	0.74	0.40	[0.14, 1.70]
Total residual deviance[b]	39.95	7.192	[27.92, 55.94]	31.95	7.96	[18.28, 49.23]
DIC[c]	155.346			151.73		
pD	21.733			26.115		

Hazard ratios (mean and SD) with credible intervals (CrI); 5-ASA: 5-aminosalicylic acid; DIC: deviance information criterion; pD: number of parameters; SD: standard deviation

[a] Compared to 36 data points.

[b] SD exceeds the 0.5 threshold.

[c] DIC is lower with the random-effects model by 3.6, therefore random-effects model will be reported.

Table 10. Clinical relapse: relative effectiveness of all pairwise comparisons

	Placebo	5-ASA	Adalimumab	Antibiotics	Budesonide	Infliximab	Probiotics	Purine analogues	Sulfasalazine
5-ASA	0.69 [0.53, 0.87]								
Adalimumab	0.11 [0.02, 0.33]	0.17 [0.02, 0.47]							

Table 10. Clinical relapse: relative effectiveness of all pairwise comparisons (*Continued*)

Antibiotics	0.98 [0.50, 1.71]	1.44 [0.71, 2.65]	16.03 [2. 50, 63.86]						
Budes- onide	0.66 [0.27, 1.34]	0.97 [0.38, 2.04]	10.96 [1. 44, 44.37]	0.74 [0.24, 1.74]					
Infliximab	0.36 [0.02, 1.74]	0.52 [0.02, 2.50]	4.40 [0.20, 23.93]	0.40 [0.02, 2.01]	0.65 [0.02, 3.31]				
Probiotic	1.11 [0.62, 1.88]	1.64 [0.86, 2.90]	17.96 [2. 84, 72.01]	1.25 [0.51, 2.59]	2.00 [0.67, 4.84]	13.91 [0. 56, 75.55]			
Purine analogues	0.75 [0.55, 1.00]	1.09 [0.82, 1.45]	11.90 [2. 29, 45.20]	0.84 [0.40, 1.57]	1.35 [0.53, 2.90]	9.15 [0.44, 48.37]	0.73 [0.37, 1.29]		
Sul- fasalazine	0.89 [0.55, 1.30]	1.31 [0.77, 2.04]	14.48 [2. 49, 55.60]	1.00 [0.43, 1.98]	1.60 [0.58, 3.58]	11.15 [0. 48, 60.37]	0.87 [0.39, 1.61]	1.22 [0.68, 1.93]	
Sul- fasalazine + pred- nisolone	1.37 [0.50, 3.07]	2.02 [0.71, 4.63]	21.95 [2. 77, 92.35]	1.55 [0.45, 3.96]	2.46 [0.61, 6.87]	16.76 [0. 61, 91.89]	1.33 [0.40, 3.34]	1.87 [0.64, 4.36]	1.61 [0.52, 3.94]

Hazard ratios (mean and standard deviation) with credible intervals. 5-ASA: 5-aminosalicylic acid

Table 11. Endoscopic relapse: relative effectiveness of all pairwise comparisons

	Placebo	5-ASA	Adalimumab	Antibiotics	Infliximab	Probiotic
5-ASA	1.22 [0.61, 2.18]					
Adalimumab	0.10 [0.01, 0.32]	0.09 [0.01, 0.27]				
Antibiotics	0.80 [0.33, 1.65]	0.75 [0.23, 1.78]	32.71 [1.86, 64. 26]			
Infliximab	0.24 [0.01, 1.20]	0.30 [0.01, 1.04]	2.81 [0.13, 13. 41]	0.42 [0.01, 1.89]		
Probiotic	1.20 [0.62, 2.19]	1.12 [0.41, 2.46]	26.31 [3.16, 94. 44]	1.88 [0.57, 4.38]	36.15 [0.85, 176.30]	
Purine analogues	0.85 [0.33, 1.61]	0.75 [0.27, 1.47]	14.40 [2.69, 51. 40]	1.37 [0.32, 3.06]	19.64 [0.69, 102.60]	0.80 [0.23, 1.74]

Hazard ratios (mean and standard deviation) with credible intervals. 5-ASA: 5-aminosalicylic acid

Table 12. Withdrawals due to adverse events: relative effectiveness of all pairwise comparisons

	Placebo	5-ASA	Adalimumab	Antibiotics	Budesonide	Infliximab	Probiotics	Purine analogues
5-ASA	1.19 [0.39, 3.14]							
Adalimumab	11.74 [0.12, 55.06]	8.62 [0.12, 45.32]						
Antibiotics	53.92 [0.43, 259.80]	61.39 [0.32, 283.20]	87.42 [0.04, 299.50]					
Budesonide	1.64 [0.17, 6.19]	1.92 [0.12, 7.39]	3.78 [0.01, 14.02]	1.02 [0.00, 4.16]				
Infliximab	6.37 [0.00, 21.74]	4.21 [0.00, 19.84]	12.53 [0.00, 19.28]	3.11 [0.00, 7.97]	21.68 [0.00, 31.10]			
Probiotic	2.44 [0.13, 9.00]	3.28 [0.09, 10.20]	13.83 [0.01, 16.96]	2.53 [0.00, 5.18]	6.38 [0.06, 16.67]	2997.00 [0.03, 1553.00]		
Purine analogues	2.51 [0.79, 7.35]	2.27 [0.86, 5.35]	3.97 [0.05, 16.47]	1.79 [0.01, 6.71]	4.45 [0.28, 19.17]	1579.00 [0.12, 2047.00]	8.39 [0.20, 25.04]	
Sulfasalazine	1.96 [0.00, 8.90]	1.97 [0.00, 9.96]	15.58 [0.00, 10.09]	2.30 [0.00, 3.47]	3.57 [0.00, 13.31]	54220.00 [0.00, 607.10]	117.10 [0.00, 14.60]	0.94 [0.00, 5.01]

Hazard ratios (mean and standard deviation) with credible intervals. 5-ASA: 5-aminosalicylic acid

Table 13. Interventions compared to reference treatment

	Clinical relapse			Endoscopic relapse			Withdrawal due to adverse events		
	Random-effects model			Random-effects model			Random-effects model		
	Mean	SD	95% CrI	Mean	SD	95% CrI	Mean	SD	95% CrI
5-ASA	0.69	0.09	[0.53, 0.87]	1.22	0.63	[0.61, 2.18]	1.19	1.10	[0.39, 3.14]
Adalimumab	0.11	0.08	[0.02, 0.33]	0.10	0.25	[0.01, 0.32]	11.74	300.8	[0.12, 55.06]

Table 13. Interventions compared to reference treatment (*Continued*)

Antibiotics	0.98	0.31	[0.50, 1.71]	0.80	1.19	[0.33, 1.65]	53.92	1058	[0.43, 259.80]
Budesonide	0.66	0.28	[0.27, 1.34]	-	-	-	1.64	11.77	[0.17, 6.19]
Infliximab	0.36	0.63	[0.02, 1.74]	0.24	1.75	[0.01, 1.20]	6.37	726.8	[9.14E-04, 21.74]
Probiotic	1.11	0.33	[0.62, 1.88]	1.20	0.53	[0.62, 2.19]	2.44	65.24	[0.13, 9.00]
Purine analogues	0.75	0.12	[0.55, 1.00]	0.85	0.54	[0.33, 1.61]	2.51	4.357	[0.79, 7.35]
Sulfasalazine	0.89	0.19	[0.55, 1.30]	-	-	-	1.96	207.6	[3.04E-04, 8.90]
Sulfasalazine + prednisolone	1.37	0.7	[0.50, 3.07]	-	-	-	-	-	-
Between-study heterogeneity	0.13	0.11	[0.01, 0.40]	0.37	0.43	[0.03, 1.58]	0.74	0.40	[0.14, 1.70]
Total residual deviance	42.21	8.223	[27.98, 60.07]	26.22	6.77	[14.62, 41.05]	31.95	7.96	[18.28, 49.23]
DIC	244.26			133.43			151.73		
pD	31.95			20.86			26.115		

Hazard ratios (mean and SD) with credible intervals (Crl); 5-ASA: 5-aminosalicylic acid; DIC: deviance information criterion; pD: number of parameters; SD: standard deviation

Table 14. Clinical relapse: ranking of treatments

Treatment code	Treatment definition	Median rank	Mean rank	Range
3	Adalimumab	1	1.28	(1, 2)
6	Infliximab	2	2.50	(1, 10)
5	Budesonide	3	4.27	(2, 10)

Table 14. Clinical relapse: ranking of treatments (*Continued*)

2	5-ASA	4	4.30	(2, 7)
8	Purine analogues	5	5.06	(3, 8)
9	Sulfasalazine	6	6.51	(3, 10)
4	Antibiotics	7	6.96	(3, 10)
1	Placebo	8	7.88	(6, 10)
7	Probiotics	8	7.90	(3, 10)
10	Sulfasalazine + prednisolone	9	8.28	(3, 10)

Table 15. Endoscopic relapse: ranking of treatments

Treatment code	Treatment definition	Median rank	Mean rank	Range
3	Adalimumab	1	1.40	(1, 2)
5	Infliximab	2	1.82	(1, 6)
4	Antibiotics	3	3.81	(2, 7)
7	Purine analogues	4	4.09	(3, 7)
1	Placebo	5	5.17	(3, 7)
6	Probiotic	6	5.76	(3, 7)
2	5-ASA	6	5.96	(3, 7)

5-aminosalicylic acid

Table 16. Withdrawals due to adverse events: ranking of treatments

Treatment code	Treatment definition	Median rank	Mean rank	Range
9	Sulfasalazine	2	2.61	(1, 9)
6	Infliximab	2	3.40	(1, 9)
2	5-ASA	4	4.31	(2, 7)

Table 16. Withdrawals due to adverse events: ranking of treatments (*Continued*)

1	Placebo	4	4.37	(2, 7)
5	Budesonide	4	4.67	(1, 9)
7	Probiotic	5	4.80	(1, 9)
3	Adalimumab	7	6.36	(1, 9)
8	Purine analogues	7	6.67	(4, 9)
4	Antibiotics	9	7.82	(2, 9)

5-aminosalicylic acid

Table 17. Overall rank of treatment and certainty of evidence

Rank	Clinical relapse	Endoscopic relapse	Withdrawal due to adverse events
1	Adalimumab	Adalimumab	Sulfasalazine
2	Infliximab	Infliximab	Infliximab
3	Budesonide	Antibiotics	5-ASA
4	5-ASA	Purine analogues	Placebo
5	Purine analogues	Placebo	Budesonide
6	Sulfasalazine	Probiotics	Probiotic
7	Antibiotics	5-ASA	Adalimumab
8	Placebo		Purine analogues
9	Probiotics		Antibiotics
10	Sulfasalazine + prednisolone		

5-aminosalicylic acid

Table 18. Clinical relapse: inconsistency model

Treatment	Network meta-analysis (consistency model)			Inconsistency model		
	Mean	SD	95% CrI	Mean	SD	95% CrI
5-ASA vs PLA	0.69	0.09	[0.53, 0.87]	0.72	1.15	[0.55, 0.94]
ANT vs PLA	0.98	0.31	[0.50, 1.71]	0.94	1.35	[0.52, 1.71]
BUD vs PLA	0.66	0.28	[0.27, 1.34]	0.61	1.49	[0.28, 1.32]
INF vs PLA	0.36	0.63	[0.02, 1.74]	1.18	2.97E+43	[9.23E-86, 2.18E+85]
PLA vs PRO	1.11	0.33	[0.62, 1.88]	1.08	1.34	[0.61, 1.92]
PLA vs PUR[a]	0.75	0.12	[0.55, 1.00]	0.66	1.21	[0.45, 0.96]
PLA vs SUL	0.89	0.19	[0.55, 1.30]	0.87	1.24	[0.55, 1.30]
PLA vs S+P	1.37	0.70	[0.50, 3.07]	1.22	1.58	[0.50, 3.07]
5-ASA vs ADA	0.17	0.12	[0.02, 0.47]	0.12	2.35	[0.02, 0.51]
5-ASA vs PUR	1.09	0.16	[0.82, 1.45]	1.28	1.23	[0.86, 1.93]
ADA vs INF	4.40	9.20	[0.20, 23.93]	1.13	6.35	[0.03, 56.77]
ADA vs PUR[a]	11.90	19.08	[2.29, 45.20]	1.39	2.27E+43	[1.68E-85, 2.67E+85]
INF vs PUR	9.15	22.87	[0.44, 48.37]	2.80	4.58	[0.18, 88.15]
Between-study heterogeneity	0.13	0.11	[0.01, 0.40]	0.13	0.11	[3.67E+3, 0.42]
Total residual deviance[b]	42.21	8.223	[27.98, 60.07]	42.61	8.52	[27.83, 61.09]
DIC	244.26			246.27		
pD	31.95			33.55		

Hazard ratios (mean and SD) with credible intervals (CrI); DIC: deviance information criterion; pD: number of parameters; SD: standard deviation; 5-ASA: 5-aminosalicylic acid; PLA: placebo; ANT: antibiotics; BUD: budesonide; INF: infliximab; PRO: probiotics; PUR: purine analogues; SUL: sulfasalzine; S+P: sulfasalazine+prednisolone; ADA: adalimumab

[a] Difference between consistency and inconsistency model.

[b] Compared to 45 data points.

Table 19. Endoscopic relapse: inconsistency model

Treatment	Network meta-analysis (consistency model)			Inconsistency model		
	Mean	SD	95% Crl	Mean	SD	95% Crl
5-ASA:PLA	1.22	0.63	[0.61, 2.18]	1.29	20.38	[0.42, 2.56]
ANT:PLA	0.80	1.19	[0.33, 1.65]	0.91	8.22	[0.27, 1.99]
PLA:PRO	1.20	0.53	[0.62, 2.19]	1.27	1.60	[0.54, 2.61]
PLA:PUR	0.85	0.54	[0.33, 1.61]	1.88	130.90	[0.25, 3.23]
5-ASA:ADA[a]	0.09	1.86	[0.01, 0.27]	0.30	94.01	[7.54E-04, 0.22]
5-ASA:PUR	0.75	0.78	[0.27, 1.47]	1.32	100.20	[0.13, 2.48]
ADA:INF	2.81	18.95	[0.13, 13.41]	2.42	209.90	[0.01, 7.09]
ADA:PUR[a]	14.40	19.78	[2.69, 51.40]	192.30	3.07E+04	[0.84, 312.70]
INF:PUR	19.64	78.72	[0.69, 102.60]	22.73	2231.00	[0.02, 51.02]
Between-study heterogeneity	0.37	0.43	[0.03, 1.58]	0.47	0.42	[0.02, 1.55]
Total residual deviance[b]	26.22	6.77	[14.62, 41.05]	26.19	7.25	[13.89, 42.17]
DIC	133.43			135.70		
pD	20.86			23.16		

Hazard ratios (mean and SD) with credible intervals (Crl); DIC: deviance information criterion; pD: number of parameters; SD: standard deviation; 5-ASA: 5-aminosalicylic acid; PLA: placebo; ANT: antibiotics; INF: infliximab; PRO: probiotics; PUR: purine analogues; ADA: adalimumab

[a] Difference between consistency and inconsistency model.

[b] Compared to 21 data points.

Table 20. Withdrawal due to adverse events: inconsistency model

	Network meta-analysis (consistency model)			Inconsistency model		
	Mean	SD	95% Crl	Mean	SD	95% Crl
5-ASA:PLA	1.19	1.10	[0.39, 3.14]	1.55	1.65	[0.63, 4.51]

Table 20. Withdrawal due to adverse events: inconsistency model (*Continued*)

ANT:PLA	53.92	1058	[0.43, 259.8]	7.73	4.68	[0.58, 264.54]
BUD:PLA	1.64	11.77	[0.17, 6.19]	1.03	2.16	[0.22, 4.85]
PLA:PRO	2.44	65.24	[0.13, 9.00]	1.07	2.43	[0.18, 6.27]
PLA:PUR	2.51	4.36	[0.79, 7.35]	1.10	1.65	[0.44, 3.30]
PLA:SUL	1.96	207.6	[3.04E-04, 8.90]	0.13	12.60	[0.00, 7.74]
5-ASA:ADA	8.62	95.82	[0.12, 45.32]	3.55	4.41	[0.18, 67.29]
5-ASA:PUR[a]	2.27	1.58	[0.86, 5.35]	3.58	1.64	[1.43, 10.17]
ADA:PUR	3.97	112.5	[0.05, 16.47]	1.23	2.97E+43	[9.23E-86, 2.95E+85]
INF:PUR	1579	5.58E+04	[0.12, 2047]	7.50	12.35	[0.13, 3010.92]
Between-study heterogeneity	0.74	0.40	[0.14, 1.70]	0.47	0.36	[0.02, 1.34]
Total residual deviance[b]	31.95	7.96	[18.28, 49.23]	30.64	7.65	[17.55, 47.43]
DIC[c]	151.73			149.36		
pD	26.12			26.06		

Hazard ratios (mean and SD) with credible intervals (Crl); DIC: deviance information criterion; pD: number of parameters; SD: standard deviation; 5-ASA: 5-aminosalicylic acid; PLA: placebo; ANT: antibiotics; INF: infliximab; PRO: probiotics; PUR: purine analogues; SUL: sulfasalzine; ADA: adalimumab

[a] Difference between consistency and inconsistency model.

[b] Compared to 36 data points.

[c] DIC inconsistency < DIC consistency indicates some level of inconsistency.

Table 21. Sensitivity analysis for clinical relapse

Network meta-analysis*	Main analysis	Fixed-effect	Allocation concealment	Blinding	Attrition	Low dose of 5-ASA	Definition of outcome	Effect size
5-ASA	0.69 [0.53, 0.87]	0.7 [0.57, 0. 85]	0.64 [0.43, 0.90]	0.73 [0.54, 0.95]	0.71 [0.53, 0.92]	0.70 [0.51, 0.92]	0.69 [0.53, 0.88]	0.69 [0.53, 0.87]
Adalimumab	0.11 [0.02, 0.33]	0.12 [0.02, 0.32]	-	-	0.12 [0.02, 0.36]	0.12 [0.01, 0.34]	0.12 [0.02, 0.35]	0.12 [0.01, 0.34]

Table 21. Sensitivity analysis for clinical relapse (*Continued*)

Antibiotics	0.98 [0.50, 1.71]	0.97 [0.54, 1.60]	1.54 [0.43, 4.02]	0.86 [0.36, 1.72]	0.87 [0.36, 1.74]	0.98 [0.50, 1.76]	0.99 [0.51, 1.73]	0.86 [0.37, 1.70]
Budesonide	0.66 [0.27, 1.34]	0.65 [0.29, 1.22]	-	-	-	0.66 [0.27, 1.35]	0.65 [0.27, 1.32]	0.65 [0.27, 1.35]
Infliximab	0.36 [0.02, 1.74]	0.33 [0.02, 1.52]	-	-	0.34 [0.01, 1.70]	0.37 [0.01, 1.74]	0.33 [0.02, 1.59]	0.35 [0.02, 1.74]
Probiotics	1.11 [0.62, 1.88]	1.09 [0.62, 1.78]	1.02 [0.47, 1.94]	0.99 [0.47, 1.83]	1.12 [0.60, 1.95]	1.12 [0.60, 1.93]	1.13 [0.62, 1.91]	1.00 [0.48, 1.80]
Purine analogues	0.75 [0.55, 1.00]	0.75 [0.58, 0.94]	0.68 [0.43, 0.98]	0.71 [0.49, 1.00]	0.75 [0.53, 1.06]	0.76 [0.54, 1.04]	0.75 [0.55, 1.01]	0.75 [0.55, 1.01]
Sulfasalazine	0.89 [0.55, 1.30]	0.91 [0.66, 1.22]	-	-	0.88 [0.52, 1.33]	0.88 [0.53, 1.32]	-	0.89 [0.55, 1.31]
Sulfasalazine + prednisolone	1.37 [0.50, 3.07]	1.35 [0.53, 2.93]	-	-	-	1.39 [0.49, 3.24]	-	1.39 [0.49, 3.23]

5-ASA: 5-aminosalicylic acid

*Random-effects model was used for the main analysis and all sensitivity analyses except the fixed-effect model. Results represent hazard ratios with 95% credible intervals.

APPENDICES

Appendix 1. Search strategies

Embase

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross over$ or cross-over$).mp.
4. placebo$.mp.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).mp.
9. (double$ adj blind$).mp.
10. (tripl$ adj blind$).mp.
11. assign$.mp.
12. allocat$.mp.
13. crossover procedure/

14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. Exp Crohn disease/
20. Crohn*.mp.
21. IBD.mp.
22. Inflammatory bowel disease*.mp.
23. or/ 19-22
24. Exp Surgery/
25. Surgical*.mp.
26. Surgical resection.mp.
27. Colectomy.mp.
28. Resection*.mp.
29. or/24-28
30. Exp Post Operation/
31. Post-operative.mp.
32. Post opera*.mp.
33. Postopera*.mp.
33. or/ 30-33
34. Exp Corticosteroids/
35. (Corticosteroid* or Budesonide or Prednisone or Prednisolone or Hydrocortisone or Methylprednisolone).mp.
36. Exp 5-ASA/
37. (5- aminosalicylic acid or 5-aminosalicylates or Aminosalicylates or Mesalamine or Mesalazine or Sulfasalazine).mp.
39. Exp Purine analogues/
40. Tumor necrosis factor inhibitor*.mp.
41. TNF-antagonist.mp.
41. (Immunomodulator* or Azathioprine or Mercaptopurine or Infliximab or Adalimumab or Certolizumab or Methotrexate or Natalizumab or Vedolizumab or Ustekinumab).mp.
42. Exp Antibiotics/
43. (Antibiotic* or Ciprofloxacin or Metronidazole).mp.
44. (Probiotic* or Prebiotic*or Supplement* or Calcium or Acetaminophen or Ibuprofen or Fiber*).mp.
45. or/34-44
46. 18 and 23 and 29 and 33 and 45

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. Exp Crohn disease/
16. Crohn*.mp.
17. IBD.mp.

18. Inflammatory bowel disease*.mp.
19. or/ 15-18
20. Exp Surgery/
21. Surgical*.mp.
22. Surgical resection.mp.
23. Colectomy.mp.
24. Resection*.mp.
25. or/20-24
26. Post operation.mp.
27. Post-operative.mp.
28. Post opera*.mp.
29. Postopera*.mp.
30. or/26-29
31. Exp Corticosteroids/
32. (Corticosteroid* or Budesonide or Prednisone or Prednisolone or Hydrocortisone or Methylprednisolone).mp.
33. Exp aminosalicylic acid/
34. (5- ASA or 5-aminosalicylates or Aminosalicylates or Mesalamine or Mesalazine or Sulfasalazine).mp.
35. Purine analogues.mp.
36. Tumor necrosis factor inhibitor*.mp.
37. TNF-antagonist.mp.
38. (Immunomodulator* or Azathioprine or Mercaptopurine or Infliximab or Adalimumab or Certolizumab or Methotrexate or Natalizumab or Vedolizumab or Ustekinumab).mp.
39. Exp Antibiotics/
40. (Antibiotic* or Ciprofloxacin or Metronidazole).mp.
41. (Probiotic* or Prebiotic*or Supplement* or Calcium or Acetaminophen or Ibuprofen or Fiber*).mp.
42. or/31-41
43. 14 and 19 and 25 and 30 and 42

Cochrane CENTRAL

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 Crohn Disease
#3 Crohn
#4 IBD
#5 #1 or #2 or #3 or #4
#6 MeSH: [Colectomy] explode all trees
#7 Surgery
#8 Surgical*
#9 Surgical resection
#10 Resection*
#11 #6 or #7 or #8 or #9 or #10
#12 Post operation
#13 Post-operative
#14 Post opera*
#15 Postopera*
#16 #12 or #13 or #14 or # 15
#17 Corticosteroid* or Budesonide or Prednisone or Prednisolone or Hydrocortisone or Methylprednisolone
#18 5- ASA or 5-aminosalicylates or Aminosalicylates or Mesalamine or Mesalazine or Sulfasalazine or Aminosalicylic acid
#19 Purine Analogues
#20 Tumor Necrosis Factor-alpha
#21 Tumor necrosis factor inhibitor*
#22 Immunomodulator* or Azathioprine or Mercaptopurine or Infliximab or Adalimumab or Certolizumab or Methotrexate or Natalizumab or Vedolizumab or Ustekinumab
#23 MeSH: [Anti-Bacterial Agents] explode all trees
#24 Antibiotic* or Ciprofloxacin or Metronidazole

#25 MeSH: [Probiotics] explode all trees
#26 Probiotic* or Prebiotic*or Supplement* or Calcium or Acetaminophen or Ibuprofen or Fiber*
#27 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28 #5 and #11 and #16 and #27

ClinicalTrials.gov/WHO ICTRP

1. Inflammatory bowel disease and surgery
2. Crohn's disease and surgery
3. Inflammatory bowel disease and resection
4. Crohn's disease and resection

Appendix 2. Quality assessment of the evidence

GRADE assessment applied network:

Risk of bias: 33% of studies in network at moderate or high risk of bias
Indirectness: 33% of studies with PICO not directly relevant to network meta-analysis question
Imprecision: 33% of the studies in the network contribute to imprecise results in the mixed and indirect evidence (determined from Appendix 6 to Appendix 11)
Heterogeneity: based on the I^2 threshold of 0.5
Consistency: if deviance information criterion (DIC) in inconsistency model < DIC in consistency model
Publication bias: suspected small-study effect in majority of the evidence in the network

CINeMA quality assessment:

*Assessment of risk of bias, indirectness, heterogeneity, and publication bias were the same as GRADE.
Imprecision: whether confidence interval or credible interval of individual contrasts include clinically important effects in either or both directions (effect estimates less than 0.75 or greater than 1.25)
Incoherence: based on discordance in direction of effect between individual contrasts in the consistency versus inconsistency model

Appendix 3. Clinical relapse: per study contribution matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Random OR																					
Mixed estimates	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5-ASA: ADA	7.29	0.94	0.00	1.10	1.57	0.00	0.00	0.00	3.96	2.96	0.00	4.19	0.00	3.99	0.00	3.15	0.00	66.33	0.45	4.09	0.00
5-ASA: PLAC	5.26	0.09	0.00	11.22	15.94	0.00	0.00	0.00	7.27	2.14	0.00	42.63	0.00	9.26	0.00	0.24	0.00	1.27	4.54	0.15	0.00

(*Continued*)

5-ASA: PUR	30.38	0.29	0.00	2.68	3.80	0.00	0.00	0.00	15.80	12.35	0.00	10.17	0.00	16.18	0.00	0.26	0.00	6.97	1.08	0.03	0.00
ADA INF	0.42	10.98	0.00	1.61	2.28	0.00	0.00	0.00	1.26	0.17	0.00	6.11	0.00	3.94	0.00	15.67	0.00	26.72	0.65	30.19	0.00
ADA PUR	7.90	2.32	0.00	0.65	0.92	0.00	0.00	0.00	4.41	3.21	0.00	2.47	0.00	6.52	0.00	2.88	0.00	63.26	0.26	5.20	0.00
ANT PLA(	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	29.11	0.00	0.00	0.00	0.00	0.00	70.89	0.00	0.00	0.00	0.00
BUD PLA(	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
INF: PLA(	1.60	12.01	0.00	0.90	1.27	0.00	0.00	0.00	2.25	0.65	0.00	3.41	0.00	9.39	0.00	58.10	0.00	5.17	0.36	4.90	0.00
INF: PUR	4.70	26.58	0.00	0.96	1.36	0.00	0.00	0.00	4.47	1.91	0.00	3.64	0.00	16.07	0.00	24.92	0.00	7.89	0.39	7.10	0.00
PLA(PRO	0.00	0.00	0.00	0.00	0.00	0.00	0.00	43.03	0.00	0.00	0.00	0.00	33.50	0.00	23.48	0.00	0.00	0.00	0.00	0.00	0.00
PLA(PUR	9.93	0.61	0.00	2.89	4.11	0.00	0.00	0.00	12.04	4.04	0.00	10.98	0.00	50.91	0.00	0.73	0.00	2.48	1.17	0.12	0.00
PLA(SUL	0.00	0.00	0.00	0.00	0.00	75.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	24.84
PLA(SUL-	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
In-direct es-ti-mate:	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

(*Continued*)

5-ASA: ANT	3.51	0.07	0.00	5.61	7.97	0.00	0.00	0.00	4.21	1.43	13.47	21.31	0.00	6.18	0.00	0.18	32.80	0.89	2.27	0.11	0.00
5-ASA: BUD	3.51	0.07	0.00	5.61	7.97	0.00	46.27	0.00	4.21	1.43	0.00	21.31	0.00	6.18	0.00	0.18	0.00	0.89	2.27	0.11	0.00
5-ASA: INF	7.58	12.86	0.00	4.12	5.86	0.00	0.00	0.00	4.57	3.08	0.00	15.66	0.00	0.05	0.00	28.66	0.00	8.58	1.67	7.31	0.00
5-ASA: PRO	3.51	0.07	0.00	5.61	7.97	0.00	0.00	19.91	4.21	1.43	0.00	21.31	15.50	6.18	10.86	0.18	0.00	0.89	2.27	0.11	0.00
5-ASA: SUL	3.51	0.07	0.00	5.61	7.97	34.77	0.00	0.00	4.21	1.43	0.00	21.31	0.00	6.18	0.00	0.18	0.00	0.89	2.27	0.11	11.49
5-ASA: SUL-	3.51	0.07	46.27	5.61	7.97	0.00	0.00	0.00	4.21	1.43	0.00	21.31	0.00	6.18	0.00	0.18	0.00	0.89	2.27	0.11	0.00
ADA ANT	0.93	0.68	0.00	2.47	3.51	0.00	0.00	0.00	2.65	0.38	9.46	9.39	0.00	10.45	0.00	3.41	23.03	28.55	1.00	4.10	0.00
ADA BUD	0.93	0.68	0.00	2.47	3.51	0.00	32.49	0.00	2.65	0.38	0.00	9.39	0.00	10.45	0.00	3.41	0.00	28.55	1.00	4.10	0.00
ADA PLA(	1.21	0.85	0.00	3.65	5.19	0.00	0.00	0.00	3.87	0.49	0.00	13.88	0.00	15.67	0.00	5.12	0.00	42.60	1.48	5.97	0.00
ADA PRO	0.93	0.68	0.00	2.47	3.51	0.00	0.00	13.98	2.65	0.38	0.00	9.39	10.88	10.45	7.63	3.41	0.00	28.55	1.00	4.10	0.00
ADA SUL	0.93	0.68	0.00	2.47	3.51	24.42	0.00	0.00	2.65	0.38	0.00	9.39	0.00	10.45	0.00	3.41	0.00	28.55	1.00	4.10	8.07
ADA SUL-	0.93	0.68	32.49	2.47	3.51	0.00	0.00	0.00	2.65	0.38	0.00	9.39	0.00	10.45	0.00	3.41	0.00	28.55	1.00	4.10	0.00

(*Continued*)

ANT BUD	0.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	14.55	0.00	0.00	0.00	0.00	0.00	35.45	0.00	0.00	0.00	0.00
ANT INF	1.25	8.12	0.00	0.69	0.97	0.00	0.00	0.00	1.60	0.51	11.91	2.60	0.00	6.26	0.00	29.05	29.02	3.97	0.28	3.77	0.00
ANT PRO	0.00	0.00	0.00	0.00	0.00	0.00	0.00	21.51	0.00	0.00	14.55	0.00	16.75	0.00	11.74	0.00	35.45	0.00	0.00	0.00	0.00
ANT PUR	6.62	0.41	0.00	1.93	2.74	0.00	0.00	0.00	6.88	2.69	12.47	7.33	0.00	25.45	0.00	0.50	30.38	1.72	0.78	0.09	0.00
ANT SUL	0.00	0.00	0.00	0.00	0.00	37.58	0.00	0.00	0.00	0.00	14.55	0.00	0.00	0.00	0.00	0.00	35.45	0.00	0.00	0.00	12.42
ANT SUL-	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	14.55	0.00	0.00	0.00	0.00	0.00	35.45	0.00	0.00	0.00	0.00
BUD INF	1.25	8.12	0.00	0.69	0.97	0.00	40.93	0.00	1.60	0.51	0.00	2.60	0.00	6.26	0.00	29.05	0.00	3.97	0.28	3.77	0.00
BUD PRO	0.00	0.00	0.00	0.00	0.00	0.00	50.00	21.51	0.00	0.00	0.00	0.00	16.75	0.00	11.74	0.00	0.00	0.00	0.00	0.00	0.00
BUD PUR	6.62	0.41	0.00	1.93	2.74	0.00	42.85	0.00	6.88	2.69	0.00	7.33	0.00	25.45	0.00	0.50	0.00	1.72	0.78	0.09	0.00
BUD SUL	0.00	0.00	0.00	0.00	0.00	37.58	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.42
BUD SUL-	0.00	0.00	50.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
INF: PRO	1.25	8.12	0.00	0.69	0.97	0.00	0.00	17.61	1.60	0.51	0.00	2.60	13.71	6.26	9.61	29.05	0.00	3.97	0.28	3.77	0.00

(*Continued*)

INF: SUL	1.25	8.12	0.00	0.69	0.97	30.76	0.00	0.00	1.60	0.51	0.00	2.60	0.00	6.26	0.00	29.05	0.00	3.97	0.28	3.77	10.17
INF: SUL-	1.25	8.12	40.93	0.69	0.97	0.00	0.00	0.00	1.60	0.51	0.00	2.60	0.00	6.26	0.00	29.05	0.00	3.97	0.28	3.77	0.00
PRO PUR	6.62	0.41	0.00	1.93	2.74	0.00	0.00	18.44	6.88	2.69	0.00	7.33	14.35	25.45	10.06	0.50	0.00	1.72	0.78	0.09	0.00
PRO SUL	0.00	0.00	0.00	0.00	0.00	37.58	0.00	21.51	0.00	0.00	0.00	0.00	16.75	0.00	11.74	0.00	0.00	0.00	0.00	0.00	12.42
PRO SUL-	0.00	0.00	50.00	0.00	0.00	0.00	0.00	21.51	0.00	0.00	0.00	0.00	16.75	0.00	11.74	0.00	0.00	0.00	0.00	0.00	0.00
PUR SUL	6.62	0.41	0.00	1.93	2.74	32.21	0.00	0.00	6.88	2.69	0.00	7.33	0.00	25.45	0.00	0.50	0.00	1.72	0.78	0.09	10.65
PUR SUL-	6.62	0.41	42.85	1.93	2.74	0.00	0.00	0.00	6.88	2.69	0.00	7.33	0.00	25.45	0.00	0.50	0.00	1.72	0.78	0.09	0.00
SUL: SUL-	0	0.00	50.00	0.00	0.00	37.58	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.42

Appendix 4. Clinical relapse: per comparison contribution matrix

Random	5-ASA: ADA	5-ASA: PLAC	5-ASA: PUR	ADA: INF	ADA: PUR	ANT: PLAC	BUD: PLAC	INF: PLAC	INF: PUR	PLAC: PRO	PLAC: PUR	PLAC: SUL	PLAC: SUL+PRE
Mixed estimates													
5-ASA: ADA	47	7.6775	14.515	4.0875	18.105	0	0	3.15	0.9375	0	4.5275	0	0
5-ASA: PLAC	0.2708	78.14	10.485	0.15	0.1208	0	0	0.2375	0.0875	0	10.5183	0	0

(*Continued*)

5-ASA: PUR	0.9567	18.6383	60.51	0.0267	0.93	0	0	0.2633	0.29	0	18.375	0	0
ADA: INF	12.0383	11.1933	0.845	30.19	14.6083	0	0	15.6717	10.975	0	4.4783	0	0
ADA: PUR	20.265	4.52	15.745	5.1983	41.67	0	0	2.8833	2.315	0	7.4033	0	0
ANT: PLAC	0	0	0	0	0	100	0	0	0	0	0	0	0
BUD: PLAC	0	0	0	0	0	0	100	0	0	0	0	0	0
INF: PLAC	3.0467	6.2433	3.1967	4.8967	1.85	0	0	58.1	12.0067	0	10.66	0	0
INF: PUR	2.6967	6.67	9.3667	7.1017	4.405	0	0	24.92	26.58	0	18.25	0	0
PLAC: PRO	0	0	0	0	0	0	0	0	0	100	0	0	0
PLAC: PUR	0.3467	20.1217	19.775	0.1233	0.47	0	0	0.7333	0.61	0	57.82	0	0
PLAC: SUL	0	0	0	0	0	0	0	0	0	0	0	100	0
Indirect estimates													
5-ASA: ANT	0.2055	39.07	6.99	0.1125	0.093	46.2655	0	0.1805	0.068	0	7.015	0	0
5-ASA: BUD	0.2055	39.07	6.99	0.1125	0.093	0	46.2655	0.1805	0.068	0	7.015	0	0
5-ASA: INF	5.02	28.715	15.0883	7.3133	2.2933	0	0	28.655	12.855	0	0.06	0	0
5-ASA: PRO	0.2055	39.07	6.99	0.1125	0.093	0	0	0.1805	0.068	46.2655	7.015	0	0

(*Continued*)

5-ASA: SUL	0.2055	39.07	6.99	0.1125	0.093	0	0	0.1805	0.068	0	7.015	46.2655	0
5-ASA: SUL+PR	0.2055	39.07	6.99	0.1125	0.093	0	0	0.1805	0.068	0	7.015	0	46.2655
ADA: ANT	15.3667	17.2112	1.8445	4.0953	13.0292	32.4912	0	3.4133	0.682	0	11.8667	0	0
ADA: BUD	15.3667	17.2112	1.8445	4.0953	13.0292	0	32.4912	3.4133	0.682	0	11.8667	0	0
ADA: PLAC	23.05	25.4525	2.4025	5.9725	19.35	0	0	5.12	0.8525	0	17.8	0	0
ADA: PRO	15.3667	17.2112	1.8445	4.0953	13.0292	0	0	3.4133	0.682	32.4912	11.8667	0	0
ADA: SUL	15.3667	17.2112	1.8445	4.0953	13.0292	0	0	3.4133	0.682	0	11.8667	32.4912	0
ADA: SUL+PR	15.3667	17.2112	1.8445	4.0953	13.0292	0	0	3.4133	0.682	0	11.8667	0	32.4912
ANT: BUD	0	0	0	0	0	50	50	0	0	0	0	0	0
ANT: INF	2.285	4.775	2.49	3.765	1.48	40.9317	0	29.05	8.1167	0	7.1067	0	0
ANT: PRO	0	0	0	0	0	50	0	0	0	50	0	0	0
ANT: PUR	0.26	13.4433	13.1833	0.0925	0.3525	42.8525	0	0.4992	0.4067	0	28.91	0	0
ANT: SUL	0	0	0	0	0	50	0	0	0	0	0	50	0
ANT: SUL+PR	0	0	0	0	0	50	0	0	0	0	0	0	50
BUD: INF	2.285	4.775	2.49	3.765	1.48	0	40.9317	29.05	8.1167	0	7.1067	0	0
BUD: PRO	0	0	0	0	0	0	50	0	0	50	0	0	0

(*Continued*)

BUD: PUR	0.26	13.4433	13.1833	0.0925	0.3525	0	42.8525	0.4992	0.4067	0	28.91	0	0
BUD: SUL	0	0	0	0	0	0	50	0	0	0	0	50	0
BUD: SUL+PR	0	0	0	0	0	0	50	0	0	0	0	0	50
INF: PRO	2.285	4.775	2.49	3.765	1.48	0	0	29.05	8.1167	40.9317	7.1067	0	0
INF: SUL	2.285	4.775	2.49	3.765	1.48	0	0	29.05	8.1167	0	7.1067	40.9317	0
INF: SUL+PR	2.285	4.775	2.49	3.765	1.48	0	0	29.05	8.1167	0	7.1067	0	40.9317
PRO: PUR	0.26	13.4433	13.1833	0.0925	0.3525	0	0	0.4992	0.4067	42.8525	28.91	0	0
PRO: SUL	0	0	0	0	0	0	0	0	0	50	0	50	0
PRO: SUL+PR	0	0	0	0	0	0	0	0	0	50	0	0	50
PUR: SUL	0.26	13.4433	13.1833	0.0925	0.3525	0	0	0.4992	0.4067	0	28.91	42.8525	0
PUR: SUL+PR	0.26	13.4433	13.1833	0.0925	0.3525	0	0	0.4992	0.4067	0	28.91	0	42.8525
SUL: SUL+PR	0	0	0	0	0	0	0	0	0	0	0	50	50

Appendix 5. Clinical relapse: CINeMA quality assessment report

Comparison	Number of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
5-ASA:ADA	1	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low

(*Continued*)

5-ASA: PLAC	5	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
5-ASA:PUR	4	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
ADA:INF	1	Some concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
ADA:PUR	1	Some concerns	Suspected	No concerns	No concerns	No concerns	Major concerns	Very low
ANT:PLAC	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:PLAC	1	No concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Low
INF:PLAC	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:PUR	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PLAC:PRO	3	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PLAC:PUR	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
PLAC:SUL	2	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
PLAC: SUL+PRE	1	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
Indirect evidence								
5-ASA: ANT	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA: BUD	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:PRO	0	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate

(*Continued*)

5-ASA:SUL	0	Major concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
5-ASA: SUL+PRE	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
ADA:ANT	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
ADA:BUD	0	No concerns	Suspected	No concerns	Some concerns	No concerns	No concerns	Low
ADA:PLAC	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
ADA:PRO	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
ADA:SUL	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
ADA: SUL+PRE	0	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	Low
ANT:BUD	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:PUR	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:SUL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT: SUL+PRE	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:INF	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:PRO	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:PUR	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

(*Continued*)

BUD:SUL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD: SUL+PRE	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:PRO	0	Some concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Low
INF:SUL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF: SUL+PRE	0	Major concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Very low
PRO:PUR	0	Some concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Very Low
PRO:SUL	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
PRO: SUL+PRE	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
PUR:SUL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PUR: SUL+PRE	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
SUL: SUL+PRE	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

Appendix 6. Endoscopic relapse: per study contribution matrix

Random OR	1	2	3	4	5	6	7	8	9	10	11	12
Mixed estimates	--	--	--	--	--	--	--	--	--	--	--	--
5-ASA: ADA	2.505	5.8829	0	0	6.7121	0	12.595	0	0	58. 1433	11. 6467	2.505

(*Continued*)

5-ASA: PLA	0.165	39.6412	0	0	45.2288	0	6.8283	0	0	7.3423	0.6293	0.165
5-ASA: PUR	0.62	13.3235	0	0	15.2015	0	28.525	0	0	39.0295	2.6805	0.62
ADA: INF	17.1458	0.8746	0	0	0.9979	0	1.8725	0	0	10.8684	7.6507	60.59
ADA: PUR	5.945	2.6079	0	0	2.9755	0	5.5833	0	0	42.7354	34.2079	5.945
ANT: PLA	0	0	0	39.958	0	0	0	0	60.042	0	0	0
INF: PUR	51.3	1.0813	0	0	1.2337	0	2.315	0	0	13.4301	9.4533	21.1867
PLA: PRO	0	0	29.8631	0	0	42.9191	0	27.2178	0	0	0	0
PLA: PUR	0.3	5.8634	0	0	6.6899	0	72.18	0	0	13.4989	1.1577	0.3
Indirect estimates	--	--	--	--	--	--	--	--	--	--	--	--
5-ASA: ANT	0.132	19.8206	0	18.822	22.6144	0	4.6695	0	28.2825	5.055	0.472	0.132
5-ASA: INF	20.8567	6.4827	0	0	7.3965	0	13.8792	0	0	28.8711	3.3864	19.1275
5-ASA: PRO	0.132	19.8206	14.0668	0	22.6144	20.2168	4.6695	12.8208	0	5.055	0.472	0.132
ADA: ANT	2.136	6.2594	0	12.7363	7.1416	0	18.4733	0	19.138	21.7536	10.2257	2.136
ADA: PLA	2.67	9.1314	0	0	10.4186	0	27.71	0	0	32.0711	15.3289	2.67
ADA: PRO	2.136	6.2594	9.5187	0	7.1416	13.6802	18.4733	8.6755	0	21.7536	10.2257	2.136
ANT: INF	16.6967	3.9735	0	11.3525	4.5335	0	19.9042	0	17.0586	11.3167	3.4398	11.7145

(*Continued*)

ANT: PRO	0	0	14. 9315	19.979	0	21. 4596	0	13. 6089	30.021	0	0	0
ANT: PUR	0.24	4.0095	0	17. 8509	4.5747	0	36.09	0	26. 8233	9.2934	0.8683	0.24
INF: PLA	25.045	5.1795	0	0	5.9096	0	29. 3217	0	0	14. 7215	4.4468	15. 3658
INF: PRO	16. 6967	3.9735	8.4844	0	4.5335	12. 1938	19. 9042	7.7329	0	11. 3167	3.4398	11. 7145
PRO: PUR	0.24	4.0095	13. 3411	0	4.5747	19. 1738	36.09	12. 1593	0	9.2934	0.8683	0.24

Appendix 7. Endoscopic relapse: per comparison contribution matrix

Random OR	5-ASA: ADA	5-ASA: PLA	5-ASA: PUR	ADA:INF	ADA:PUR	ANT:PLA	INF:PUR	PLA:PRO	PLA:PUR
Mixed estimates									
5-ASA: ADA	37.56	12.595	11.07	2.505	21.16	0	2.505	0	12.595
5-ASA: PLA	1.3083	84.87	5.52	0.165	1.1433	0	0.165	0	6.8283
5-ASA: PUR	5.49	28.525	31.35	0.62	4.87	0	0.62	0	28.525
ADA:INF	3.2458	1.8725	1.3733	60.59	13.9	0	17.1458	0	1.8725
ADA:PUR	10.1883	5.5833	4.605	5.945	62.15	0	5.945	0	5.5833
ANT:PLA	0	0	0	0	0	100	0	0	0
INF:PUR	4.0117	2.315	1.6967	21.1867	17.175	0	51.3	0	2.315
PLA:PRO	0	0	0	0	0	0	0	100	0
PLA:PUR	2.4033	12.5533	10.15	0.3	2.1033	0	0.3	0	72.18
Indirect estimates									
5-ASA: ANT	0.9895	42.435	3.68	0.132	0.8575	47.1045	0.132	0	4.6695

(*Continued*)

5-ASA: INF	12.975	13.8792	13.13	19.1275	6.1525	0	20.8567	0	13.8792
5-ASA: PRO	0.9895	42.435	3.68	0.132	0.8575	0	0.132	47.1045	4.6695
ADA: ANT	11.16	13.401	2.241	2.136	18.5783	31.8743	2.136	0	18.4733
ADA:PLA	16.74	19.55	2.81	2.67	27.85	0	2.67	0	27.71
ADA:PRO	11.16	13.401	2.241	2.136	18.5783	0	2.136	31.8743	18.4733
ANT:INF	5.465	8.507	3.042	11.7145	6.2495	28.4112	16.6967	0	19.9042
ANT:PRO	0	0	0	0	0	50	0	50	0
ANT:PUR	1.8175	8.5842	6.7667	0.24	1.5775	44.6742	0.24	0	36.09
INF:PLA	7.2867	11.0892	3.8025	15.3658	8.0792	0	25.045	0	29.3217
INF:PRO	5.465	8.507	3.042	11.7145	6.2495	0	16.6967	28.4112	19.9042
PRO:PUR	1.8175	8.5842	6.7667	0.24	1.5775	0	0.24	44.6742	36.09

Appendix 8. Endoscopic relapse: CINeMA quality assessment report

Comparison	Number of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
5-ASA vs ADA	1	Some concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Very low
5-ASA vs PLA	2	No concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Low
5-ASA vs PUR	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
ADA vs INF	1	Major concerns	Suspected	No concerns	Major concerns	No concerns	No concerns	Very low
ADA vs PUR	2	Major concerns	Suspected	No concerns	No concerns	No concerns	Some concerns	Very low

(*Continued*)

ANT vs PLA	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF vs PUR	1	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
PLA vs PRO	3	No concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Low
PLA vs PUR	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Indirect evidence								
5-ASA: ANT	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:INF	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
5-ASA:PRO	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:ANT	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Very low
ADA:PLA	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Very low
ADA:PRO	0	Some concerns	Suspected	No concerns	No concerns	Some concerns	No concerns	Very low
ANT:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:PUR	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:PLA	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Low
INF:PRO	0	Some concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Very low
PRO:PUR	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

Appendix 9. Withdrawal due to adverse events: per comparison contribution matrix

Random OR	5-ASA: ADA	5-ASA: PLA	5-ASA: PUR	ADA: PUR	ANT: PLA	BUD: PLA	INF: PUR	PLA: PRO	PLA: PUR	PLA:SUL
Mixed estimates										
5-ASA: ADA	37.33	5.6533	22.855	28.5083	0	0	0	0	5.6533	0
5-ASA: PLA	0.43	60.5	19.105	0.43	0	0	0	0	19.535	0
5-ASA: PUR	1.205	13.21	71.18	1.205	0	0	0	0	13.21	0
ADA: PUR	15.885	3.15	12.735	65.08	0	0	0	0	3.15	0
ANT: PLA	0	0	0	0	100	0	0	0	0	0
BUD: PLA	0	0	0	0	0	100	0	0	0	0
INF: PUR	0	0	0	0	0	0	100	0	0	0
PLA: PRO	0	0	0	0	0	0	0	100	0	0
PLA: PUR	0.37	16.855	16.485	0.37	0	0	0	0	65.92	0
PLA:SUL	0	0	0	0	0	0	0	0	0	100
Indirect estimates										
5-ASA: ANT	0.3225	30.25	12.7367	0.3225	43.3092	0	0	0	13.0592	0
5-ASA: BUD	0.3225	30.25	12.7367	0.3225	0	43.3092	0	0	13.0592	0
5-ASA: INF	0.8033	8.8033	35.59	0.8033	0	0	45.1967	0	8.8033	0
5-ASA: PRO	0.3225	30.25	12.7367	0.3225	0	0	0	43.3092	13.0592	0
5-ASA: SUL	0.3225	30.25	12.7367	0.3225	0	0	0	0	13.0592	43.3092

(*Continued*)

ADA: ANT	12.0133	13.8858	1.8725	20.6958	32.7092	0	0	0	18.8233	0
ADA: BUD	12.0133	13.8858	1.8725	20.6958	0	32.7092	0	0	18.8233	0
ADA: INF	10.8525	2.3625	8.49	32.54	0	0	43.3925	0	2.3625	0
ADA: PLA	18.02	20.5167	2.4967	30.7317	0	0	0	0	28.235	0
ADA: PRO	12.0133	13.8858	1.8725	20.6958	0	0	0	32.7092	18.8233	0
ADA: SUL	12.0133	13.8858	1.8725	20.6958	0	0	0	0	18.8233	32.7092
ANT: BUD	0	0	0	0	50	50	0	0	0	0
ANT: INF	0.222	8.4645	8.2425	0.222	30.4378	0	30.4378	0	21.9733	0
ANT: PRO	0	0	0	0	50	0	0	50	0	0
ANT: PUR	0.2775	11.2675	10.99	0.2775	44.2275	0	0	0	32.96	0
ANT: SUL	0	0	0	0	50	0	0	0	0	50
BUD: INF	0.222	8.4645	8.2425	0.222	0	30.4378	30.4378	0	21.9733	0
BUD: PRO	0	0	0	0	0	50	0	50	0	0
BUD: PUR	0.2775	11.2675	10.99	0.2775	0	44.2275	0	0	32.96	0
BUD: SUL	0	0	0	0	0	50	0	0	0	50
INF:PLA	0.2775	11.2675	10.99	0.2775	0	0	44.2275	0	32.96	0
INF: PRO	0.222	8.4645	8.2425	0.222	0	0	30.4378	30.4378	21.9733	0

(*Continued*)

INF:SUL	0.222	8.4645	8.2425	0.222	0	0	30.4378	0	21.9733	30.4378
PRO: PUR	0.2775	11.2675	10.99	0.2775	0	0	0	44.2275	32.96	0
PRO: SUL	0	0	0	0	0	0	0	50	0	50
PUR: SUL	0.2775	11.2675	10.99	0.2775	0	0	0	0	32.96	44.2275

Appendix 10. Withdrawals due to adverse events: per study contribution matrix

Random OR	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Mixed estimates	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5-ASA: ADA	8.0627	0	1.8453	0.5543	0	0	1.8848	8.8754	0	5.1689	0	4.1943	2.8106	66.6037	0
5-ASA: PLA	6.7398	0	19.7475	5.932	0	0	20.1707	24.7467	0	4.3208	0	14.4932	2.3494	1.4998	0
5-ASA: PUR	25.1107	0	4.3118	1.2952	0	0	4.4042	25.4422	0	16.0981	0	9.8006	8.7534	4.7937	0
ADA: PUR	4.4926	0	1.0282	0.3089	0	0	1.0502	4.9455	0	2.8802	0	2.337	1.5661	81.3915	0
ANT: PLA	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
BUD: PLA	0	0	0	0	22.192	0	0	0	77.808	0	0	0	0	0	0
INF: PUR	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0

(*Continued*)

PLA: PRO	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
PLA: PUR	5. 8155	0	5. 5015	1. 6526	0	0	5. 6195	25. 4568	0	3. 7283	0	48. 9065	2. 0273	1. 2921	0
PLA: SUL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100
Indirect estimates	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5-ASA: ANT	4. 4932	0	9. 8737	2.966	0	0	10. 0853	14. 0655	0	2. 8805	43. 3092	9. 6887	1. 5663	1. 0715	0
5-ASA: BUD	4. 4932	0	9. 8737	2.966	9. 6112	0	10. 0853	14. 0655	33. 698	2. 8805	0	9. 6887	1. 5663	1. 0715	0
5-ASA: INF	12. 5553	45. 1967	2. 8734	0. 8632	0	0	2.935	13. 8208	0	8. 0491	0	6. 5313	4. 3767	2. 7985	0
5-ASA: PRO	4. 4932	0	9. 8737	2.966	0	43. 3092	10. 0853	14. 0655	0	2. 8805	0	9. 6887	1. 5663	1. 0715	0
5-ASA: SUL	4. 4932	0	9. 8737	2.966	0	0	10. 0853	14. 0655	0	2. 8805	0	9. 6887	1. 5663	1. 0715	43. 3092
ADA: ANT	0. 6606	0	4. 5324	1. 3615	0	0	4. 6295	8. 7161	0	0. 4235	32. 7092	13. 9652	0. 2303	32. 7718	0
ADA: BUD	0. 6606	0	4. 5324	1. 3615	7. 2588	0	4. 6295	8. 7161	25. 4503	0. 4235	0	13. 9652	0. 2303	32. 7718	0
ADA: INF	2. 9951	43. 3925	0. 7711	0. 2316	0	0	0. 7877	3. 4282	0	1. 9201	0	1. 7528	1. 0441	43. 6768	0
ADA: PLA	0. 8808	0	6. 6967	2. 0117	0	0	6. 8403	12. 9158	0	0. 5646	0	20. 9478	0.307	48. 8353	0
ADA: PRO	0. 6606	0	4. 5324	1. 3615	0	32. 7092	4. 6295	8. 7161	0	0. 4235	0	13. 9652	0. 2303	32. 7718	0

(*Continued*)

ADA: SUL	0.6606	0	4.5324	1.3615	0	0	4.6295	8.7161	0	0.4235	0	13.9652	0.2303	32.7718	32.7092
ANT: BUD	0	0	0	0	11.096	0	0	0	38.904	0	50	0	0	0	0
ANT: INF	2.9078	30.4378	2.7629	0.8299	0	0	2.8221	9.9017	0	1.8641	30.4378	16.3022	1.0136	0.72	0
ANT: PRO	0	0	0	0	0	50	0	0	0	0	50	0	0	0	0
ANT: PUR	3.877	0	3.6778	1.1048	0	0	3.7566	14.143	0	2.4855	44.2275	24.4533	1.3515	0.923	0
ANT: SUL	0	0	0	0	0	0	0	0	0	0	50	0	0	0	50
BUD: INF	2.9078	30.4378	2.7629	0.8299	6.7548	0	2.8221	9.9017	23.6831	1.8641	0	16.3022	1.0136	0.72	0
BUD: PRO	0	0	0	0	11.096	50	0	0	38.904	0	0	0	0	0	0
BUD: PUR	3.877	0	3.6778	1.1048	9.815	0	3.7566	14.143	34.4125	2.4855	0	24.4533	1.3515	0.923	0
BUD: SUL	0	0	0	0	11.096	0	0	0	38.904	0	0	0	0	0	50
INF: PLA	3.877	44.2275	3.6778	1.1048	0	0	3.7566	14.143	0	2.4855	0	24.4533	1.3515	0.923	0
INF: PRO	2.9078	30.4378	2.7629	0.8299	0	30.4378	2.8221	9.9017	0	1.8641	0	16.3022	1.0136	0.72	0
INF: SUL	2.9078	30.4378	2.7629	0.8299	0	0	2.8221	9.9017	0	1.8641	0	16.3022	1.0136	0.72	30.4378
PRO: PUR	3.877	0	3.6778	1.1048	0	44.2275	3.7566	14.143	0	2.4855	0	24.4533	1.3515	0.923	0
PRO: SUL	0	0	0	0	0	50	0	0	0	0	0	0	0	0	50

(*Continued*)

PUR: SUL	3.877	0	3. 6778	1. 1048	0	0	3. 7566	14. 143	0	2. 4855	0	24. 4533	1. 3515	0.923	44. 2275

Appendix 11. Withdrawal due to adverse events: CINeMA quality assessment report

Comparison	Number of studies	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
5-ASA:ADA	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:PLA	4	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:PUR	5	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Low
ADA:PUR	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
ANT:PLA	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:PLA	2	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:PUR	1	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
PLA:PRO	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PLA:PUR	2	No concerns	Undetected	No concerns	Major concerns	Some concerns	No concerns	Low
PLA:SUL	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
Indirect evidence								
5-ASA: ANT	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA: BUD	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

(*Continued*)

5-ASA:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
5-ASA:SUL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:ANT	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:BUD	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:PLA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ADA:SUL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:BUD	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:PUR	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
ANT:SUL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:INF	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
BUD:PUR	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

(*Continued*)

BUD:SUL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:PLA	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:PRO	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
INF:SUL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PRO:PUR	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PRO:SUL	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
PUR:SUL	0	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

CONTRIBUTIONS OF AUTHORS

- Zipporah Iheozor-Ejiofor co-ordinated the review; extracted data and contacted authors; checked the quality of data extraction; performed statistical analysis; checked the quality of the statistical analysis; interpreted data; undertook and checked quality assessment; produced the first draft of the review; contributed to writing and editing the review; made an intellectual contribution to the review; contributed to previous version of the review; approved the final review prior to submission.

- Morris Gordon performed screening of titles and abstracts and full-text articles, checked the quality of data extraction and interpreted data; contributed to writing and editing the review; made an intellectual contribution to the review; contributed to previous version of the review; approved the final review prior to submission.

- Andrew Clegg made an intellectual contribution to the review; contributed to previous version of the review; approved the final review prior to submission.

- Suzanne C Freeman performed statistical analysis; checked the quality of the statistical analysis; contributed to editing the review; made an intellectual contribution to the review; approved the final review prior to submission.

- Teuta Gjuladin-Hellon performed screening of titles and abstracts and full-text articles; extracted data; contributed to writing the review; made an intellectual contribution to the review; approved the final review prior to submission.

- John K MacDonald checked the quality assessment; contributed to editing the review; made an intellectual contribution to the review; contributed to previous version of the review; approved the final review prior to submission.

- Anthony K Akobeng initiated and conceptualised the review; contributed to previous version of the review; made an intellectual contribution to the review; approved the final review prior to submission.

DECLARATIONS OF INTEREST

- Zipporah Iheozor-Ejiofor: None known.

- Morris Gordon has received travel fees from Abbott, Nutricia, BioGaia, Ferring, Allergan, and Tillots to attend international scientific and training meetings such as DDW, Advances in IBD, ESPGHAN, BSPGHAN, and Cochrane-focused international events. None of these companies has had any involvement in any works completed by Morris Gordon, and he has had no payments for any other activities.

- Andrew Clegg: None known.

- Suzanne C Freeman: None known

- Teuta Gjuladin-Hellon: None known.

- John K MacDonald: None known.

- Anthony K Akobeng: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Inclusion criteria was limited to studies with a minimum of 3 months of treatment to ensure consistency with similar reviews (Gjuladin-Hellon 2019a; Gjuladin-Hellon 2019b) in the Cochrane IBD portfolio

- According to the protocol, studies that recruited participants in any sort of relapse (clinical, endoscopic, or histologic, etc.) were to be excluded. We included a study that recruited people in endoscopic relapse (Reinisch 2010). To avoid transitivity, we only included it in the network meta-analysis (NMA) for the outcome withdrawal due to adverse events.

- We carried out an all-domain risk of bias where we assigned four ratings (very high, high, low and unclear), but grouped 'low' and 'unclear' risk of bias together following methods reported in Norman 2018.

- We intended to generate funnel plot (Assessment of reporting biases); assess for statistical heterogeneity using 90% significance level, use the ifplot command on Stata 2017 as a local approach for evaluating inconsistency and use Chi² as global approach for evaluating inconsistency (Subgroup analysis and investigation of heterogeneity). None of these was feasible with our Markov Chain Monte Carlo (MCMC) model; alternative methods were used instead.

- We have reported the risk ratio (RR) for pairwise comparisons and the hazard ratio (HR) for the NMA as planned due to the nature of the data. Our first primary outcome was dichotomous, and the second was survival data. The included studies did not report on time to relapse as survival data, but reported this as a dichotomous outcome instead (i.e. number of relapses). The NMA was carried out in such a way that takes time into account using the clog-log link. The pairwise comparison, on the other hand, did not take time into account and has been analysed using the RR as intended.

- Although we intended to contact leaders in the field and drug companies to identify additional studies, we did not do so.