ECCO GRADE CD Treatment Guidelines

Supplementary Material

Content:

Section 1: Description of the process

Three domains for medical treatment of CD were identified: 1) induction therapy; 2) maintenance therapy, and 3) therapy of perianal fistulizing disease. All panelists were assigned to 3 working groups coordinated by 1-2 working group leaders under the supervision of 2 main Guideline coordinators. The panelists first formulated a series of specific questions in the PICO format (Population, Intervention, Comparator, Outcomes) that were deemed to be clinically important for the medical treatment of CD. The outcomes of all PICO questions were subsequently graded as "not important", "important" or "critical" during a face-to-face kickoff meeting in Vienna in March 2018, using a Delphi consensus process. The list of outcomes and the grading of each outcome are displayed in *Section 2*.

Based on the PICO statements, a broad systematic literature search was prepared by librarians using a predetermined protocol, for each PICO and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Relevant studies were searched in the PubMed/MEDLINE, and EMBASE (Excerpta Medica Database), and Cochrane CENTRAL databases (time period was restricted to the last 20 years). Only studies published in English were eligible. An outline of the detailed search strategy performed for each PICO is in each database is available in *Section 3.*

Two reviewers independently conducted an initial screen of abstracts for eligibility and evaluated the full-text articles of identified abstracts for final eligibility, according to the PICO. Disagreements were resolved by consensus and, if necessary, by involvement of the working group leader and/or coordinator.

Each working group member was responsible to systematically review and summarize the evidence on every outcome, for a given questions, in order to compile a Summary of Findings (SoF) table for each question. The SOF tables generated for each PICO are available in section 4. When needed data from individual studies were pooled and analysed using random-effects meta-analysis as appropriate. The forest plots from these analysis are displayed in Section 5.

Section 2: List of outcomes

Outcome	Importance	Median	Disagreement index
Common outcomes			
Clinical response	Critical	7	0.37
Clinical remission	Critical	8	0.29
Biochemical improvement	Important, but not critical	6	0.32
Biochemical remission	Important, but not critical	6	0.33
Quality of life	Critical	8	0.29
PRO response	Important, but not critical	6	0.58
PRO remission	Critical	7	0.65
Radiologic improvement	Important, but not critical	5	0.52
Radiologic remission	Important, but not critical	5	0.97
Steroid free clinical remission	Critical	8	0.22
ANY adverse events AEs	Critical	7	0.22
Serious adverse events SAEs	Critical	9	0.13
Adverse events leading to treatment discontinuation	Critical	7	0.29
Serious infections	Critical	8	0.22
Cancer	Critical	8	0.13
Hematologic malignancies	Critical	8	0.29
Working Group 1 (Induction of remission)			
Endoscopic response WG1	Important, but not critical	6	0.52
Endoscopic remission WG1	Important, but not critical	6	0.58
Mucosal healing WG1	Important, but not critical	6	0.65
Regain of clinical response WG1	Critical	7	0.22
Working Group 2 (Maintainance of remission)			
Endoscopic response WG2	Important, but not critical	6	0.52
Endoscopic remission WG2	Critical	7	0.37
Mucosal healing WG2	Critical	8	0.24
Regain of clinical response WG2	Critical	7	0.22
Working Group 3 (Management of perianal disease)			
Fistula healing	Critical	8	0.13

Outcome	Importance	Median	Disagreement index
Maintenance of clinical fistula remission	Critical	8	0.13
Resolution of perianal sepsis	Critical	8	0.22
Successful restoration of continuity	Critical	7	0.37
Working Group 4 (Surgery in abdominal CD)			
Length of hospital stay	Important, but not critical	5	0.85
Reduced pain	Important, but not critical	6	0.22
Improved cosmesis	Important, but not critical	5	0.85
Stoma free survival	Critical	7	0.33
Temporary stoma	Important, but not critical	6	0.50
Minor surgical complications	Important, but not critical	6	0.52
Major surgical complications	Critical	8	0.29
Post operative sepsis	Critical	8	0.16
Surgical recurrence WG4	Critical	7	0.16
Sepsis control	Critical	7	0.16
Symptomatic improvement	Critical	7	0.48
Time to clinical recurrence	Critical	7	0.29
Time to endoscopic recurrence[1]	Critical	7	0.22
Time to surgical recurrence	Critical	7	0.16
Length of intestinal resection	Critical	7	0.37

1 After re-vote. Original voting was: median = 6, DI = 0.52

Section 3: Search Strategy

A systematic literature search was conducted by a qualified team of librarians using predetermined search terms in Pubmed/Medline, Embase and Cochrane Central. The search strings for each PICO question are available for consultation in Supplementary Files 1, 2 and 3.

Section 4: Summary of Findings Tables (SOF)

Summary Of Findings Tables Referring To Induction Treatment Of Crohn's Disease (Section 1 In Manuscript)

Summary of Findings Table 1 (5-aminosalycilates and sulphasalazine versus placebo)

PICO question: 5-ASA compound vs. placebo
P: Adult patients, mild Crohn's disease with activity, small and/or large intestine
I: 5-ASA compound, any preparation, any dose
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 930 (7 studies) 10–18 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	94/357 (26.3%)	182/573 (31.8%)	RR, 1.28 (0.97–1.69)	263 per 1000	74 more per 1000 (from 7 fewer to 182 more)
Withdrawals due to adverse events (critical outcome)											
N: 698 (6 studies) 10–18 weeks	Not serious	Not serious	Not serious	Serious[1]	Undetected	Moderate	22/282 (7.8%)	50/416 (12.0%)	RR, 1.13 (0.70–1.84)	78 per 1000	18 more per 1000 (from 23 fewer to 65 more)

References:

-- Crohn's II study. In: Ford A, Kane S, Khan K, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. American Journal of Gastroenterology 2011; 106: 617–629.
-- Tremaine W, Schroeder K, Harrison J, et al. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. Journal of Clinical Gastroenterology 1994; 19: 278–282.
-- Singleton J, Hanauer S, Gitnick G, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. Gastroenterology 1993; 104: 1293–1301.
-- Rasmussen S, Lauritsen K, Tage-Jensen U, et al. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. Scandinavian Journal of Gastroenterology 1987; 22: 877–883.
-- PEACE study: a study with pentasa in patients with active crohn's disease. Available from http://clinicaltrials.gov/show/NCT00862121.
-- Malchow H, Ewe K, Brandes J, et al. European Cooperative Crohn's disease study (ECCDS): results of drug treatment. Gastroenterology 1984; 86: 249–266.
-- Summers R, Switz D, Sessions J, et al. National Cooperative Crohn's disease study: results of drug treatment. Gastroenterology 1979; 77: 847–869.

Footnotes:
[1] Sparse data (72 events)

Comment: Evidence was sought also for clinical response, PRO response and remission, biochemical and endoscopic improvement, and serious adverse events; however, data were insufficient.

Abbreviations: 5-ASA, 5-aminosalicylic acid; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 2 (Budesonide versus placebo)

PICO question: Budesonide vs. placebo
P: Adult patients, mild Crohn's disease with activity, small and/or large intestine
I: Budesonide, any preparation, dose of 9 mg daily
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 379 (3 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	29/133 (21.8%)	115/246 (46.7%)	RR, 1.93 (1.37–2.73)	218 per 1000	204 more per 1000 (from 81 more to 378 more)
Clinical response (critical outcome)											
N: 252 (2 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	22/67 (32.8%)	108/185 (58.4%)	RR, 1.46 (1.03–2.07)	328 per 1000	151 more per 1000 (from 10 more to 352 more)
Adverse events (critical outcome)											
N: 379 (3 studies) 8 weeks	Not serious	Not serious	Serious[1]	Not serious	Undetected	Moderate	44/133 (33.1%)	115/246 (46.7%)	RR, 0.98 (0.77–1.25)	331 per 1000	6 fewer per 1000 (from 75 fewer to 81 more)

Reference: Rezaie A, Kuenzig ME, Benchimol EI, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2015; Issue 6. Art. No.: CD000296.

Footnotes:
[1] The meta-analysis reported the impact of the intervention of interest on corticosteroid-related adverse events, which is an outcome closely related to, but different from adverse events.

Comment: Evidence was sought also for PRO response, PRO remission, biochemical improvement, endoscopic improvement, serious adverse events; however, data were insufficient.

Abbreviations: RR, risk ratio; CI, confidence interval.

Summary of Findings Table 3 - (Budesonide versus 5-aminsosalicylates)

PICO question: Budesonide vs. 5-aminosalicylate compound
P: Adult patients, mild Crohn's disease with activity, small and/or large intestine
I: Budesonide, any preparation, dose of 9 mg daily
C: 5-aminosalicylate compound, any preparation

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 601 (3 studies) 8 weeks	Not serious	Serious[1]	Not serious	Not serious	Undetected	Moderate	146/298 (49.0%)	187/303 (61.7%)	RR, 1.30 (0.98–1.72)	490 per 1000	146 more per 1000 (from 10 fewer to 354 more)
Clinical response (critical outcome)											
N: 601 (3 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	172/298 (57.7%)	212/303 (70.0%)	RR, 1.22 (1.03–1.45)	577 per 1000	127 more per 1000 (from 15 more to 259 more)
Any adverse events, AEs (critical outcome)											
N: 601 (3 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	161/298 (54.0%)	151/303 (49.8%)	RR, 0.91 (0.79–1.05)	540 per 1000	48 fewer per 1000 (from 115 fewer to 29 more)
Serious adverse events, SAEs (critical outcome)											
N: 294 (2 studies) 8 weeks	Not serious	Not serious	Not serious	Serious[2]	Undetected	Moderate	18/145 (12.4%)	14/149 (9.4%)	RR, 0.94 (0.24–3.75)	124 per 1000	7 fewer per 1000 (from 95 fewer to 341 more)

References:
-- Thomsen OO, Cortot A, Jewell D, et al. A comparison of budesonide and mesalamine for active Crohn's disease. New England Journal of Medicine 1998; 339(6): 370–374.
-- Tromm A, Bunganic I, Tomsova E, et al. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. Gastroenterology 2011; 140(2): 425–434.e1.
-- Yokoyama T, Ohta A, Motoya S, et al. Efficacy and safety of oral budesonide in patients with active Crohn's disease in Japan: A multicenter, double-blind, randomized, parallel-group phase 3 study. Inflammatory Intestinal Diseases 2018; 2(3): 154–162.

Footnotes:
[1] Heterogeneity: $I^2 = 62\%$
[2] Sparse data (32 events)

Comment: We also searched for evidence regarding PRO response and remission, biochemical and endoscopic improvement; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 4 (Systemic corticosteroid (Prednisolone, prednisone) versus placebo)

PICO question: Systemic corticosteroid (prednisolone, prednisone) vs. placebo
P: Adult patients, Crohn's Disease with moderate to severe activity, small and/or large intestine
I: Systemic corticosteroid (prednisolone, prednisone)
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical response (critical outcome)											
N: 105 (1 study) 6 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	31/58 (53.4%)	44/47 (93.6%)	RR, 1.75 (1.36–2.25)	534 per 1000	401 more per 1000 (from 192 more to 668 more)
Clinical remission (critical outcome)											
N: 267 (2 studies) 6–17 weeks	Not serious	Not serious	Not serious	Serious[2]	Undetected	Moderate	42/135 (31.1%)	79/132 (59.8%)	RR, 1.99 (1.51–2.64)	311 per 1000	308 more per 1000 (from 159 more to 510 more)
Any adverse events, AEs (critical outcome)											
N: 162 (1 study) 17 weeks	Not serious	N/A	Not serious	Serious[3]	N/A	Moderate	5/77 (6.5%)	27/85 (31.8%)	RR, 4.89 (1.98–12.07)	65 per 1000	253 more per 1.000 (from 64 more to 719 more)

Reference: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008: CD006792.

Footnotes:
[1] Sparse data (75 events).
[2] Sparse data (121 events).
[3] Sparse data (32 events) and very wide CI.

Comment: Evidence was sought also for quality of life, PRO response, biochemical improvement, endoscopic improvement and serious adverse events; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 5 (Azathioprine or Mercaptopurine (Thiopurines) versus no treatment)

PICO question: Azathioprine or Mercaptopurine (Thiopurines) vs. no treatment
P: Adult patients, Crohn's disease with moderate to severe activity, small and/or large intestinal
I: Azathioprine or Mercaptopurine (Thiopurines)
C: No treatment

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical response (critical outcome)											
N: 73 (3 studies) 8–24 weeks	Not serious	Serious[1]	Not serious	Very serious[2]	Undetected	Very low	7/26 (26.9%)	12/28 (42.9%)	RR, 1.87 (0.44–7.96)	269 per 1000	234 more per 1000 (from 151 fewer to 731 more)
Clinical remission (critical outcome)											
N: 380 (5 studies) 12–17 weeks	Not serious	Not serious	Not serious	Serious[3]	Undetected	Moderate	68/183 (37.2%)	95/197 (48.2%)	RR, 1.23 (0.97–1.55)	372 per 1000	85 more per 1000 (from 11 fewer to 204 more)
Any adverse events, AEs (critical outcome)											
N: 80 (1 study)	Not serious	N/A	Not serious	Serious[4]	Undetected	Moderate	24/28 (85.7%)	36/52 (69.2%)	RR, 0.81 (0.64–1.02)	857 per 1000	163 fewer per 1000 (from 17 more to 309 fewer)
Serious adverse events, SAEs (critical outcome)											
N: 216 (2 studies)	Not serious	Not serious	Not serious	Very serious[5]	Undetected	Low	4/105 (3.8%)	15/111 (13.5%)	RR, 2.57 (0.92–7.13)	38 per 1000	60 more per 1000 (from 3 fewer to 234 more)

Reference: Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD000545.
Footnotes:
[1] Heterogeneity: $I^2 = 69\%$
[2] Sparse data (19 events) and very wide CIs
[3] Sparse data (163 events)
[4] Sparse data (60 events)
[5] Sparse data (19 events) and very wide CIs

Comment: We also searched for evidence regarding PRO response, PRO remission, biochemical improvement, endoscopic improvement, and radiologic improvement; however, data were insufficient.
Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 6 (Methotrexate versus no treatment)

PICO question: Methotrexate vs. no treatment
P: Adult patients, Crohn's disease with moderate to severe activity, small and/or large intestinal
I: Methotrexate
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 141 (1 study) 16 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	9/47 (19.1%)	37/94 (39.4%)	RR, 2.06 (1.09–3.89)	191 per 1000	202 more per 1000 (from 16 more to 554 more)
Withdrawal due to adverse events (critical outcome)											
N: 141 (1 study) 16 weeks	Not serious	N/A	Not serious	Very serious[2]	N/A	Low	1/47 (2.1%)	16/94 (17.0%)	RR, 8.00 (1.09–58.51)	21 per 1000	149 more per 1000 (from 2 more to 979 more)

Reference: Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. New England Journal of Medicine 1995; 332(5): 292–297.

Footnotes:
[1] Sparse data (46 events)
[2] Sparse data (17 events) and very wide CIs

Comment: We also searched for evidence regarding PRO response, PRO remission, biochemical improvement, endoscopic improvement, and radiologic improvement; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 7 (Methotrexate versus thiopurine)

PICO question: Methotrexate vs. thiopurine
P: Adult patients, Crohn's disease with moderate to severe activity, small and/or large intestinal
I: Methotrexate
C: AZA/6-MP

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 143 (3 studies) 24–36 weeks	Serious[1]	Not serious	Not serious	Serious[2]	Undetected	Low	45/75 (60.0%)	37/68 (54.4%)	RR, 0.87 (0.70–1.09)	600 per 1000	77 fewer per 1000 (from 182 fewer to 54 more)
Any adverse events, AEs (critical outcome)											
N: 54 (1 study) 24 weeks	Serious[3]	N/A	Not serious	Serious[4]	N/A	Low	7/27 (25.9%)	17/27 (63.0%)	RR, 2.43 (1.21–4.89)	259 per 1000	371 more per 1000 (from 54 more to 741 more)

Reference: McDonald JWD, Wang Y, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No. CD003459.

Footnotes:
[1] Methods of allocation concealment were unclear in all 3 studies, and problems with blinding existed in 2 studies
[2] Sparse data (82 events)
[3] Rated as high risk of bias for blinding (investigator blind design)
[4] Sparse data (24 events) and wide CI

Comment: We also searched for evidence regarding PRO response and remission, biochemical, endoscopic and radiologic improvement, serious adverse events, and quality of life; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 8 (TNF inhibitor (Infliximab or adalimumab or certolizumab) versus placebo)

PICO question: TNF inhibitor (infliximab or adalimumab or certolizumab) vs placebo
P: Adult patients, Crohn's disease with moderate to severe activity, with inadequate response to conventional therapy
I: TNF inhibitor (infliximab or adalimumab or certolizumab)
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 1771 (6 studies) 4–12 weeks	Not serious	Serious[1]	Not serious	Not serious	Undetected	Moderate	150/882 (17.0%)	227/889 (25.5%)	RR, 1.66 (1.17–2.36)	170 per 1000	112 more per 1000 (from 29 more to 231 more)
Clinical response (critical outcome)											
N: 1771 (6 studies) 4–12 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	246/882 (27.9%)	346/889 (38.9%)	RR, 1.43 (1.17–1.73)	279 per 1000	120 more per 1000 (from 47 more to 204 more)
Endoscopic improvement (important outcome)											
N: 171 (2 studies) 10–12 weeks	Not serious	Not serious	Not serious	Very serious[2]	Undetected	Low	8/77 (10.4%)	27/94 (28.7%)	RR, 3.25 (0.53–19.8)	104 per 1000	233 more per 1000 (from 49 fewer to 896 more)
Adverse events (critical outcome)											
N: 2219 (7 studies) 4–12 weeks	Not serious	N/R	Not serious	Not serious	Undetected	High	630/940 (67.0%)	863/1279 (67.5%)	RR, 0.99 (0.90–1.08)	670 per 1000	7 fewer per 1000 (from 67 fewer to 54 more)

References:

-- Stidham R, Lee T, Higgins P, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Alimentary Pharmacology & Therapeutics 2014; 39(12): 1349–1362.
-- Cholapranee A, Hazlewood G, Kaplan G, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Alimentary Pharmacology & Therapeutics 2017; 45(10): 1291–1302.
-- Ford A, Sandborn W, Khan K, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. American Journal of Gastroenterology 2011; 106(4): 644–659.

Footnotes:
[1] Heterogeneity: $I^2 = 63.5\%$
[2] Sparse data (35 events) and very wide CI
Comment: Evidence was sought also for PRO response and remission, biochemical and radiologic improvement, and quality of life; however, data were insufficient.
Abbreviations: TNF, tumor necrosis factor; N/R, not reported; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 9 (Adalimumab with thiopurine versus adalimumab without thiopurine)

PICO question: TNF inhibitor with thiopurine vs TNF inhibitor without thiopurine
P: Adult patients, Crohn's disease with moderate to severe activity, with inadequate response to conventional therapy
I: TNF inhibitor (**adalimumab**) with thiopurine
C: TNF inhibitor (**adalimumab**) without thiopurine

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 176 (1 study) 26 weeks	Not serious	N/A	Not serious	Not serious	N/A	High	61/85 (71.8%)	62/91 (68.1%)	RR, 0.95 (0.78–1.15)	718 per 1000	36 fewer per 1000 (from 156 fewer to 109 more)
Endoscopic improvement (important outcome)											
N: 115 (1 study) 26 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	37/58 (63.8%)	48/57 (84.2%)	RR, 1.32 (1.06–1.65)	638 per 1000	204 more per 1000 (from 35 more to 362 more)
Adverse events leading to drug discontinuation (critical outcome)											
N: 176 (1 study) 52 weeks	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	19/85 (22.4%)	21/91 (23.1%)	RR, 1.03 (0.60–1.78)	224 per 1000	7 more per 1000 (from 90 fewer to 175 more)

Reference: Matsumoto T, et al. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. Journal of Crohn's and Colitis 2016; 10: 1259–1266.

Footnotes:
[1] Sparse data (85 events)
[2] Sparse data (40 events)

Comment: Evidence was sought also for clinical response, PRO response and remission, biochemical improvement, quality of life, adverse events, and serious adverse events; however, data were insufficient.

Abbreviations: TNF, tumor necrosis factor; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 10 (Infliximab with thiopurine versus Infliximab without thiopurine)

PICO question: TNF inhibitor with thiopurine vs TNF inhibitor without thiopurine
P: Adult patients, Crohn's disease with moderate to severe activity, with inadequate response to conventional therapy
I: TNF inhibitor (**infliximab**) with thiopurine
C: TNF inhibitor (**infliximab**) without thiopurine

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 338 (1 study) 26 weeks	Not serious	N/A	Not serious	Not serious	N/A	High	75/169 (44.4%)	96/169 (56.8%)	RR, 1.28 (1.03–1.59)	444 per 1000	124 more per 1000 (from 15 more to 260 more)
Endoscopic improvement (important outcome)											
N: 200 (1 study) 26 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	28/93 (30.1%)	47/107 (43.9%)	RR, 1.46 (1.00–2.13)	301 per 1000	138 more per 1000 (from 0 more to 339 more)
Adverse events, AEs (critical outcome)											
N: 342 (1 study) N/R	Not serious	N/A	Not serious	Not serious	N/A	High	145/163 (89.0%)	161/179 (89.9%)	RR, 1.01 (0.94–1.09)	890 per 1000	10 more per 1000 (from 53 fewer to 78 more)
Serious adverse events, SAEs (critical outcome)											
N: 342 (1 study) 52 weeks	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	39/163 (23.9%)	27/179 (15.1%)	RR, 0.63 (0.41–0.98)	239 per 1000	88 fewer per 1000 (from 4 fewer to 142 fewer)

Reference: Colombel JF, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. New England Journal of Medicine 2010; 362: 1383–1395.

Footnotes:
[1] Sparse data (75 events)
[2] Sparse data (66 events)

Comment: Evidence was sought also for clinical response, PRO remission and response, biochemical improvement, and quality of life; however, data were insufficient.

Abbreviations: TNF, tumor necrosis factor; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 11 (Ustekinumab versus placebo)

PICO question: Ustekinumab vs placebo
P: Adult patients, Crohn's disease with moderate to severe activity, ileal and/or colonic, with inadequate response to conventional therapy
I: Ustekinumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 1947 (4 studies) 6 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	76/615 (12.4%)	283/1332 (21.2%)	RR, 1.76 (1.40–2.22)	124 per 1000	94 more per 1000 (from 49 more to 151 more)
Clinical response (critical outcome)											
N: 1947 (4 studies) 6 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	200/615 (32.5%)	670/1332 (50.3%)	RR, 1.56 (1.38–1.77)	325 per 1000	183 more per 1000 (from 123 more to 250 more)
Endoscopic improvement (important outcome)											
N: 252 (2 studies) 8 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	29/97 (29.9%)	74/155 (47.7%)	RR, 1.60 (1.13–2.26)	299 per 1000	178 more per 1000 (from 39 more to 376 more)
Adverse events, AEs (critical outcome)											
N: 2024 (4 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	407/637 (63.9%)	860/1387 (62.0%)	RR, 0.96 (0.90–1.03)	639 per 1000	23 fewer per 1000 (from 64 fewer to 22 more)
Serious adverse events, SAEs (critical outcome)											
N: 1997 (4 studies) 8 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	41/637 (6.4%)	71/1360 (5.2%)	RR, 0.79 (0.54–1.15)	64 per 1000	14 fewer per 1000 (from 30 fewer to 10 more)

References:
-- MacDonald JK, Nguyen TM, Khanna R, et al. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No. CD007572.
-- Rutgeerts P, Gasink C, Chan D, et al. Efficacy of ustekinumab for inducing endoscopic healing in patients with Crohn's disease. Gastroenterology 2018; 155(4): 1045–1058.
Footnote:
[1] Sparse data (103 events)
Comment: Evidence was sought also for PRO response and remission, biochemical improvement, and quality of life; however, data were insufficient.
Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 12 (Vedolizumab versus placebo)

PICO question: Vedolizumab vs. placebo
P: Adult patients, Crohn's Disease with moderate to severe activity, small and/or large intestine
I: Vedolizumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical response (critical outcome)											
N: 969 (3 studies) 6–10 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	106/413 (25.7%)	227/556 (40.8%)	RR, 1.55 (1.14–2.11)	257 per 1000	141 more per 1000 (from 36 more to 285 more)
Clinical remission (critical outcome)											
N: 969 (3 studies) 6–10 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	49/413 (11.9%)	135/556 (24.3%)	RR, 2.01 (1.50–2.71)	119 per 1000	120 more per 1000 (from 59 more to 203 more)
Serious adverse events, SAEs (critical outcome)											
N: 969 (3 studies) 6–10 weeks	Not serious	Not serious	Not serious	Serious[1]	Undetected	Moderate	35/413 (8.5%)	49/556 (8.8%)	RR, 0.94 (0.61–1.45)	85 per 1000	5 fewer per 1000 (from 33 fewer to 42 more)

Reference: Chandar AK, Singh S, Murad MH, Peyrin-Biroulet L, Loftus EV. Efficacy and safety of natalizumab and vedolizumab for the management of Crohn's disease: a systematic review and meta-analysis. Inflammatory Bowel Diseases 2015; 21(7): 1695-1708.

Footnotes:
[1] Sparse data (84 events)

Comment: Evidence was sought also for quality of life, PRO response, biochemical improvement, and endoscopic improvement; however, data were insufficient.

Abbreviations: RR, risk ratio; CI, confidence interval.

Summary of Findings Table 13 (Ustekinumab versus Vedolizumab)

PICO question: Ustekinumab vs vedolizumab
P: Adult patients, Crohn's disease with moderate to severe activity, with prior anti-TNF failure
I: Ustekinumab
C: Vedolizumab

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 1249 (4 studies) 6 weeks	Not serious	Not serious	Very serious[1]	Serious[2]	N/A	Very low	35/263 (13.3%)	62/380 (16.3%)	RR, 1.16 (0.54–2.48)	133 per 1000	21 more per 1000 (from 61 fewer to 197 more)
Clinical response (critical outcome)											
N: 1249 (4 studies) 6 weeks	Not serious	Not serious	Very serious[1,3]	Serious[2]	N/A	Very low	87/263 (33.1%)	136/380 (35.8%)	RR, 1.14 (0.65–1.99)	331 per 1000	46 more per 1000 (from 116 fewer to 327 more)
Adverse events, AEs (critical outcome)											
N: 1541 (4 studies) 6 weeks	Not serious	Not serious	Very serious[1]	Serious[2]	N/A	Very low	241/429 (56.2%)	244/380 (64.2%)	RR, 1.00 (0.82–1.23)	562 per 1000	0 more per 1000 (from 101 fewer to 129 more)
Serious adverse events, SAEs (critical outcome)											
N: 1541 (4 studies) 6 weeks	Not serious	Not serious	Very serious[1]	Serious[2]	N/A	Very low	33/429 (7.7%)	27/380 (7.1%)	RR, 0.95 (0.43–2.12)	77 per 1000	4 fewer per 1000 (from 44 fewer to 86 more)

Reference: Kawalec P, Moćko P. An indirect comparison of ustekinumab and vedolizumab in the therapy of TNF-failure Crohn's disease patients. Journal of Comparative Effectiveness Research 2018; 7(2): 101–111.

Footnotes:
[1] Evidence comes from indirect treatment comparisons
[2] Indirect treatment comparisons typically suffer from low power
[3] Clinical response was defined as a ≥100 point decrease in the Crohn's disease activity index (rather than ≥70)

Comment: Evidence was sought also for PRO response and remission, biochemical and endoscopic improvement, and quality of life; however, data were insufficient.

Abbreviations: TNF, tumor necrosis factor; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary Of Findings Tables Referring To Maintenance Treatment Of Crohn's Disease (Section 2 In Manuscript)

Summary of Findings Table 14 (5-aminosalicylates and sulphasalazine versus placebo)

PICO question: Is treatment with 5-aminosalicylates effective for the maintenance of remission in patients with CD?
P: CD patients in remission
I: 5-ASA or sulphasalazine (all doses)
C: No treatment OR placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 2014 (11 studies) 12 months	Not serious	Not serious	Not serious	Not serious	Undetected	High	472/1016 (46.5%)	472/998 (47.3%)	RR, 1.03 (0.92–1.16)	465 per 1000	16 more per 1000 (from 35 fewer to 73 more)
Serious adverse events, SAEs (critical outcome)											
N: 445 (2 studies) 12 months	Not serious	N/A	Not serious	Very serious[1]	N/A	Low	1/220 (0.5%)	2/225 (0.9%)	RR, 1.93 (0.18–21.1)	5 per 1000	4 more per 1000 (from 4 fewer to 91 more)

Reference: Akobeng AK, Zhang D, Gordon M, et al. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews 2016; Issue 9. Art. No.: CD003715.

Footnote:
[1] Very sparse data (3 events)

Comment: Evidence was sought also for steroid-free clinical remission, endoscopic remission, PRO remission, radiological remission, biochemical remission and quality of life; however, data were insufficient.

Abbreviations: CD, Crohn's disease; 5-ASA, 5-aminosalicylic acid; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 15 (Treatment with thiopurines for maintenance of remission in patients with steroid-dependent CD?)

PICO question: Is treatment with thiopurines effective for the maintenance of remission in patients with steroid-dependent CD?
P: Patients with steroid-dependent CD in remission
I: Thiopurines (azathioprine or mercaptopurine)
C: No treatment OR placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 489 (6 studies) 6–18 months	Not serious	Not serious	Not serious	Not serious	Undetected	High	166/269 (61.7%)	161/220 (73.2%)	RR, 1.19 (1.05–1.34)	617 per 1000	117 more per 1000 (from 31 more to 210 more)
Serious adverse events, SAEs (critical outcome)											
N: 556 (4 studies) 6–18 months	Not serious	Not serious	Not serious	Serious[1]	Undetected	Moderate	9/311 (2.9%)	22/245 (9.0%)	RR, 2.45 (1.22–4.90)	29 per 1000	42 more per 1000 (from 6 more to 113 more)

Reference: Chande N, Patton PH, Tsoulis DJ, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2015; Issue 10. Art. No.: CD000067.

Footnote:
[1] Sparse data (31 events)

Comment: Evidence was sought also for steroid-free clinical remission, endoscopic remission, PRO remission, radiological remission, biochemical remission and quality of life; however, data were insufficient.

Abbreviations: CD, Crohn's disease; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 16 (Treatment with thiopurines in newly diagnosed CD (i.e., early administration of azathioprine in patients without steroid-dependence)

PICO question: Is treatment with thiopurines effective in newly diagnosed CD (i.e. early administration of azathioprine in patients without steroid-dependence)?
P: Patients with newly diagnosed CD, without steroid-dependence
I: Thiopurines (azathioprine or mercaptopurine)
C: No treatment OR placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 131 (1 study) 18 months	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	32/63 (50.8%)	44/68 (64.7%)	RR, 1.27 (0.94–1.72)	508 per 1000	139 more per 1000 (from 28 fewer to 365 more)
Steroid-free clinical remission (critical outcome)											
N: 131 (1 study) 18 months	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	23/63 (36.5%)	30/68 (44.1%)	RR, 1.21 (0.79–1.84)	365 per 1000	76 more per 1000 (from 76 fewer to 307 more)
Serious adverse events, SAEs (critical outcome)											
N: 131 (1 study) 18 months	Not serious	N/A	Not serious	Very serious[3]	N/A	Low	7/63 (11.1%)	14/68 (20.6%)	RR, 1.85 (0.80–4.29)	111 per 1000	95 more per 1000 (from 22 fewer to 366 more)

Reference: Panés J, López-Sanromán A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology 2013; 145(4): 766–774.e1.

Footnotes:
[1] Sparse data (76 events)
[2] Sparse data (53 events)
[3] Sparse data (21 events) and wide CI

Comment: Evidence was sought also for endoscopic remission, PRO remission, radiological remission, biochemical remission and quality of life; however, data were insufficient.

Abbreviations: CD, Crohn's disease; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 17 (Treatment with methotrexate for the maintenance of remission in patients with steroid-dependent CD)

PICO question: Is treatment with methotrexate effective for the maintenance of remission in patients with steroid-dependent CD?
P: Patients with steroid-dependent CD in remission
I: Methotrexate (any dose)
C: No treatment OR placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission/Steroid-free clinical remission (critical outcome)											
N: 76 (1 study) 40 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	14/36 (38.9%)	26/40 (65.0%)	RR, 1.67 (1.05–2.67)	389 per 1000	261 more per 1000 (from 18 more to 649 more)

Reference: Feagan B, Fedorak R, Irvine E, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. New England Journal of Medicine 2000; 342: 1627–1632.

Footnotes:
[1]Sparse data (40 events)

Comment: We also searched for evidence regarding endoscopic remission, PRO remission, radiological remission, biochemical remission, serious adverse events and quality of life; however, data were insufficient.

Abbreviations: CD, Crohn's disease; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 18 (Anti- TNFs versus placebo)

PICO question: Is maintenance treatment with anti-TNFs appropriate for CD patients achieving remission with anti-TNFs?
P: CD patients having achieved remission with anti-TNFs
I: TNF-inhibitors (infliximab, adalimumab, certolizumab)
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 1690 (5 studies) 24–30 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	High	153/839 (18.2%)	278/851 (32.7%)	RR, 1.78 (1.51–2.09)	182 per 1000	142 more per 1000 (from 93 more to 199 more)
Endoscopic remission (critical outcome)											
N: 163 (2 studies) 52–54 weeks	Not serious	Not serious	Not serious	Serious[1]	Undetected	Moderate	1/75 (1.3%)	28/88 (31.8%)	RR, 19.7 (3.5–110.8)	13 per 1000	249 more per 1000 (from 33 more to 987 more)

References:
-- Stidham R, Lee T, Higgins P, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Alimentary Pharmacology and Therapeutics 2014; 39(12): 1349–1362.
-- Cholapranee A, Hazlewood G, Kaplan G, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Alimentary Pharmacology and Therapeutics 2017; 45(10): 1291–1302.

Footnote:
[1] Sparse data (29 events) and very wide CI.

Comment: Evidence was sought also for steroid-free clinical remission, PRO remission, radiological and biochemical remission, quality of life, and serious adverse events; however, data were insufficient.

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 19 (Vedolizumab versus placebo)

PICO question: Is maintenance treatment with vedolizumab appropriate for CD patients achieving remission with vedolizumab?
P: CD patients having achieved remission with vedolizumab
I: Vedolizumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 307 (1 study) 46 weeks	Not serious	N/A	Not serious	Not serious	N/A	High	33/153 (21.6%)	60/154 (39.0%)	RR, 1.81 (1.26–2.59)	216 per 1000	174 more per 1000 (from 56 more to 343 more)
Steroid-free clinical remission (critical outcome)											
N: 164 (1 study) 46 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	13/82 (15.9%)	26/82 (31.7%)	RR, 2.00 (1.11–3.61)	159 per 1000	159 more per 1000 (from 17 more to 414 more)
Serious adverse events, SAEs (critical outcome)											
N: 307 (1 study) 46 weeks	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	23/153 (15.0%)	28/154 (18.2%)	RR, 1.21 (0.73–2.00)	150 per 1000	31 more per 1000 (from 41 fewer to 150 more)

Reference: Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. New England Journal of Medicine 2013; 369: 711–721.

Footnotes:
[1] Sparse data (39 events)
[2] Sparse data (51 events)

Comment: Evidence was sought also for endoscopic remission, PRO remission, radiological remission, biochemical remission and quality of life; however, data were insufficient.

Abbreviations: CD, Crohn's disease; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 20 (Ustekinumab versus placebo)

PICO question: Is maintenance treatment with ustekinumab appropriate for CD patients achieving remission with ustekinumab?
P: CD patients having achieved remission with ustekinumab
I: Ustekinumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 388 (1 study) 44 weeks	Not serious	N/A	Not serious	Not serious	N/A	High	47/131 (35.9%)	131/257 (51.0%)	RR, 1.42 (1.10–1.84)	359 per 1000	151 more per 1000 (from 36 more to 301 more)
Steroid-free clinical remission (critical outcome)											
N: 388 (1 study) 44 weeks	Not serious	N/A	Not serious	Not serious	N/A	High	39/131 (29.8%)	115/257 (44.7%)	RR, 1.50 (1.12–2.02)	298 per 1000	149 more per 1000 (from 36 more to 304 more)
Endoscopic remission (important outcome)											
N: 70 (1 study) 44 weeks	Not serious	N/A	Not serious	Very serious[1]	N/A	Low	1/24 (4.2%)	5/46 (10.9%)	RR, 2.61 (0.32–21.08)	42 per 1000	67 more per 1000 (from 28 fewer to 837 more)
Serious adverse events, SAEs (critical outcome)											
N: 396 (1 study) 44 weeks	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	20/133 (15.0%)	29/263 (11.0%)	RR, 0.73 (0.43–1.25)	150 per 1000	41 fewer per 1000 (from 86 fewer to 38 more)

References:
-- Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. New England Journal of Medicine 2016; 375: 1946-1960.
-- Rutgeerts P, Gasink C, Chan D, et al. Efficacy of ustekinumab for inducing endoscopic healing in patients with Crohn's disease. Gastroenterology 2018; 155: 1045-1058.

Footnotes:
[1] Sparse data (6 events) and wide CI
[2] Sparse data (49 events)

Comment: We also searched for evidence regarding PRO remission, radiological remission, biochemical remission and quality of life; however, data were insufficient.

Abbreviations: CD, Crohn's disease; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 21 (Proactive therapeutic drug monitoring (TDM) approach versus standard symptom-based approach)

PICO question: In CD patients in clinical remission under anti-TNF treatment, is the proactive therapeutic drug monitoring (TDM) approach more effective than the standard symptom-based approach?
P: CD patients in clinical remission under anti-TNF treatment.
I: TDM approach (according to serum anti-TNF trough levels)
C: Symptom-based approach

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates			Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group	Relative effect (95% CI)	Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 173 (1 study) 52 weeks	Not serious	N/A	Serious[1]	Not serious	N/A	Moderate	45/82 (54.9%)	57/91 (62.6%)	RR, 1.14 (0.89–1.47)	549 per 1000	78 more per 1000 (from 62 fewer to 257 more)
Steroid-free clinical remission (critical outcome)											
N: 122 (1 study) 40 weeks	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	16/40 (40.0%)	25/82 (30.5%)	RR, 0.76 (0.46–1.26)	400 per 1000	96 fewer per 1000 (from 216 fewer to 104 more)
Endoscopic remission (critical outcome)											
N: 122 (1 study) 40 weeks	Not serious	N/A	Not serious	Serious[3]	N/A	Moderate	21/40 (52.5%)	42/82 (51.2%)	RR, 0.98 (0.68–1.40)	525 per 1000	11 fewer per 1000 (from 168 fewer to 210 more)
Biochemical remission (critical outcome)											
N: 173 (1 study) 52 weeks	Not serious	N/A	Serious[1]	Not serious	N/A	Moderate	45/82 (54.9%)	57/91 (62.6%)	RR, 1.14 (0.89–1.47)	549 per 1000	78 more per 1000 (from 62 fewer to 257 more)
Serious adverse events, SAEs (critical outcome)											
N: 122 (1 study) 40 weeks	Not serious	N/A	Not serious	Serious[4]	N/A	Moderate	11/40 (27.5%)	28/82 (34.1%)	RR, 1.24 (0.69–2.23)	275 per 1000	66 more per 1000 (from 85 fewer to 338 more)

References:
-- D'Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. Gastroenterology 2018; 154(5): 1343–1351.
-- Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015; 148(7): 1320–1329.e3
Footnotes:
[1] The study measured the impact of the intervention of interest on a composite outcome (clinical and biochemical remission) that is closely related to, but different from our outcome.
[2] Sparse data (41 events)
[3] Sparse data (63 events)
[4] Sparse data (39 events)
Comment: We also searched for evidence regarding PRO remission, radiological remission, and quality of life; however, data were insufficient.
Abbreviations: CD, Crohn's disease; TDM, therapeutic drug monitoring; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 22 (Therapeutic drug monitoring (TDM) approach versus standard symptom-based approach in patients with secondary loss of response to Anti-TNF)

PICO question: In CD patients having lost response to an anti-TNF agent, is the therapeutic drug monitoring (TDM) approach more effective than the standard symptom-based approach?
P: CD patients having lost response to an anti-TNF agent
I: Anti-TNF dose optimization or switching (to a different anti-TNF or to a drug with a different mechanism of action) according to serum anti-TNF trough levels/anti-drug antibodies
C: Anti-TNF dose optimization according to symptoms

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Regain of clinical response (critical outcome)											
N: 69 (1 study) 12 weeks	Serious[1]	N/A	Not serious	Serious[2]	N/A	Low	19/36 (52.8%)	19/33 (57.6%)	RR, 1.09 (0.71–1.67)	528 per 1000	48 more per 1000 (from 152 fewer to 354 more)

Reference: Steenholdt C, Brynskov J, Thomsen OØ, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2014; 63(6): 919–927.

Footnotes:
[1] Single-blind study
[2] Sparse data (38 events)

Comment: We also searched for evidence regarding endoscopic remission, PRO remission, radiological remission, biochemical remission, quality of life and serious adverse events; however, data were insufficient.

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 23 (Cessation of thiopurines monotherapy for patients in long-term remission)

PICO question: For CD patients in long-term remission on thiopurine maintenance therapy, should cessation of treatment be considered?
P: CD patients in long-term remission on thiopurine maintenance therapy
I: Cessation of treatment
C: Continuation of treatment

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical relapse (critical outcome)											
N: 215 (4 studies) 12–24 months	Not serious	Not serious	Not serious	Serious[1]	Undetected	Moderate	14/104 (13.5%)	36/111 (32.4%)	RR, 2.39 (1.38–4.13)	135 per 1000	188 more per 1000 (from 51 more to 423 more)
Serious adverse events, SAEs (critical outcome)											
N: 134 (2 studies) 12–18 months	Not serious	Not serious	Not serious	Very serious[2]	Undetected	Low	2/64 (3.1%)	0/70 (0.0%)	RR, 0.32 (0.04–2.92)	31 per 1000	21 fewer per 1000 (from 30 fewer to 60 more)

Reference: Boyapati RK, Torres J, Palmela C, Parker CE, Silverberg OM, Upadhyaya SD, Nguyen TM, Colombel JF. Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD012540.

Footnotes:
[1] Sparse data (50 events)
[2] Sparse data (2 events) and very wide CIs

Comment: We also searched for evidence regarding steroid-free clinical remission; however, data were insufficient.

Abbreviations: CD, Crohn's disease; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 24 (Cessation of thiopurines when used in combination therapy with Infliximab, in patients in long-term remission)

PICO question: If long-term remission has been achieved with the combination of anti-TNF therapy and immunosuppressants in treatment naïve CD patients, can anti-TNF monotherapy be recommended?
P: CD patients in long-term remission on combination of anti-TNF therapy and immunosuppressants in treatment naïve CD patients
I: Continuation of combination treatment
C: Anti-TNF monotherapy: **infliximab**

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical relapse (critical outcome)											
N: 111 (2 studies) 12–24 months	Serious[1]	Not serious	Serious[2]	Serious[3]	N/A	Very low	27/55 (49.1%)	27/56 (48.2%)	RR, 1.02 (0.68–1.52)	491 per 1000	10 more per 1000 (from 156 fewer to 257 more)
Serious adverse events, SAEs (critical outcome)											
N: 80 (1 study) 24 months	Serious[1]	N/A	Not serious	Very serious[4]	N/A	Very low	3/40 (7.5%)	3/40 (7.5%)	RR, 1.00 (0.21–4.66)	75 per 1000	0 more per 1000 (from 59 fewer to 275 more)

Reference: Boyapati RK, Torres J, Palmela C, Parker CE, Silverberg OM, Upadhyaya SD, Nguyen TM, Colombel JF. Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD012540.

Footnotes:
[1] High risk of bias for blinding
[2] Definition of relapse varied between studies, and differed from our outcome of interest
[3] Sparse data (54 events)
[4] Very sparse data (6 events) and wide CIs

Comment: Evidence was sought also for steroid-free clinical remission; however, data were insufficient.

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 25 (Cessation of thiopurines when used in combination therapy with Adalimumab, in patients in long-term remission)

PICO question: If long-term remission has been achieved with the combination of anti-TNF therapy and immunosuppressants in treatment naïve CD patients, can anti-TNF monotherapy be recommended?
P: CD patients in long-term remission on combination of anti-TNF therapy and immunosuppressants in treatment naïve CD patients
I: Continuation of combination treatment
C: Anti-TNF monotherapy: **adalimumab**

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Clinical remission (critical outcome)											
N: 1885 (9 studies) 56 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	Low[1]	408/1026 (39.8%)	356/859 (41.4%)	RR, 1.01 (0.91–1.13)	398 per 1000	6 more per 1000 (from 37 fewer to 53 more)
Serious adverse events, SAEs (critical outcome)											
N: 3274 (8 studies) 56 weeks	Not serious	Not serious	Not serious	Not serious	Undetected	Low[1]	128/1743 (7.3%)	101/1531 (6.6%)	RR, 0.88 (0.62–1.26)	73 per 1000	9 fewer per 1000 (from 28 fewer to 19 more)

Reference: Chalhoub JM, Rimmani HH, Gumaste VV, Sharara AI. Systematic review and meta-analysis: adalimumab monotherapy versus combination therapy with immunomodulators for induction and maintenance of remission and response in patients with Crohn's disease. Inflammatory Bowel Diseases 2017; 23(8): 1316–1327.

Footnotes:
[1] Evidence from observational studies starts as low quality.

Comment: Evidence was sought also for steroid-free clinical remission; however, data were insufficient.

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; RR, risk ratio; CI, confidence interval.

Summary Of Findings Tables Referring To the Treatment of Complex Fistulising Perianal Disease (Section 3 In Manuscript)

Summary of Findings Table 26 (Infliximab versus placebo)

PICO question: Infliximab vs placebo
P: Patients with Crohn's disease complex perianal fistulae
I: Infliximab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Fistula healing (critical outcome)											
N: 94 (1 study) 18 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	4/31 (12.9%)	29/63 (46.0%)	RR, 3.57 (1.38–9.25)	129 per 1000	331 more per 1000 (from 48 more to 871 more)
Maintenance of clinical fistula healing (critical outcome)											
N: 195 (1 study) 54 weeks	Not serious	N/A	Not serious	Serious[2]	N/A	Moderate	19/99 (19.2%)	33/96 (34.4%)	RR, 1.79 (1.10–2.92)	192 per 1000	152 more per 1000 (from 19 more to 369 more)
Serious adverse events, SAEs (critical outcome)											
N: 376 (2 studies) 18–54 weeks	Not serious	Serious[3]	Not serious	Serious[4]	N/A	Low	33/175 (18.9%)	24/201 (11.9%)	RR, 1.31 (0.11–15.25)	189 per 1000	59 more per 1000 (from 167 fewer to 811 more)

References:
-- Present D, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. New England Journal of Medicine 1999; 340: 1398–1405.
-- Sands B, Anderson F, Bernstein C, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. New England Journal of Medicine 2004; 350: 876–885.

Footnotes:
[1] Sparse data (33 events) and wide CI
[2] Sparse data (52 events)
[3] Heterogeneity: $I^2 = 57\%$
[4] Sparse data (57 events) and very wide CI

Comment: Evidence was sought also for quality of life; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 27 (Adalimumab vs placebo)

PICO question: Adalimumab vs placebo
P: Patients with Crohn's disease complex perianal fistulae
I: Adalimumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Fistula healing (critical outcome)											
N: 117 (1 study) 56 weeks	Not serious	N/A	Serious[1]	Serious[2]	N/A	Low	6/47 (12.8 %)	23/70 (32.9%)	RR, 2.57 (1.13–5.84)	128 per 1000	201 more per 1000 (from 17 more to 618 more)
Serious adverse events, SAEs (critical outcome)											
N: 117 (1 study) 56 weeks	Not serious	N/A	Serious[1]	Very serious[3]	N/A	Very low	5/47 (10.6%)	9/70 (12.9%)	RR, 1.21 (0.43–3.38)	106 per 1000	22 more per 1000 (from 60 fewer to 253 more)

Reference: Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009; 58(7): 940–948.

Footnotes:
[1] The study population suffered enterocutaneous and/or perianal fistula
[2] Sparse data (29 events)
[3] Sparse data (14 events) and wide CI

Comment: Evidence was sought also for maintenance of clinical fistula healing, resolution of perianal sepsis, stoma-free survival, and quality of life; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 28 (Ustekinumab vs placebo)

PICO question: Ustekinumab vs placebo
P: Patients with Crohn's disease complex perianal fistulae
I: Ustekinumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Induction of fistula remission (critical outcome)											
N: 238 (1 study) 8 weeks	Not serious	N/A	Not serious	Serious[1]	N/A	Moderate	10/77 (13.0%)	37/161 (23.0%)	RR, 1.77 (0.93–3.37)	130 per 1000	100 more per 1000 (from 9 fewer to 308 more)

Reference: Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2018; 16(12): 1879–1892.

Footnote:
[1] Sparse data (47 events)

Comment: Evidence was sought also for maintenance of fistula remission, serious adverse events, resolution of perianal sepsis, stoma-free survival, and quality of life; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 29 (Vedolizumab vs placebo)

PICO question: Vedolizumab vs placebo
P: Patients with Crohn's disease complex perianal fistulae
I: Vedolizumab
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Fistula healing (critical outcome)											
N: 45 (1 study) 8 weeks	No serious	N/A	No serious	Very serious[1]	N/A	Low	2/13 (15.4%)	11/32 (34.4%)	RR, 2.23 (0.57–8.72)	154 per 1000	190 more per 1000 (from 66 fewer to 846 more)

References:
-- Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 2018; 16: 1879-1892.
-- Feagan BG, Schwartz D, Danese S, et al. Efficacy of vedolizumab in fistulising Crohn's disease: exploratory analyses of data from GEMINI 2. Journal of Crohn's and Colitis 2018; 12: 621-626.

Footnotes:
[1] Sparse data (13 events) and very wide CI

Comment: Evidence was sought also for maintenance of clinical fistula healing, serious adverse events, quality of life, resolution of perianal sepsis, and stoma free survival; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 30 (Antibiotics vs placebo)

PICO question: Antibiotics vs placebo
P: Patients with Crohn's disease complex perianal fistulae
I: Antibiotics
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Fistula healing (critical outcome)											
N: 25 (1 study) 10 weeks	Not serious	N/A	Not serious	Very serious[1]	N/A	Low	1/8 (12.5%)	3/17 (17.6%)	RR, 1.41 (0.17–11.54)	125 per 1000	51 more per 1000 (from 103 fewer to 875 more)

Reference: Thia K, Mahadevan U, Feagan B, et al. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. Inflammatory Bowel Diseases 2009; 15: 17–24.

Footnote:
[1] Sparse data (4 events) and very wide CI

Comment: Evidence was sought also for maintenance of clinical fistula healing, resolution of perianal sepsis, stoma-free survival, and quality of life; however, data were insufficient.

Abbreviations: N/A, not applicable; RR, risk ratio; CI, confidence interval.

Summary of Findings Table 31 (Thiopurines (azathioprine or 6-mercaptopurine) versus placebo)

PICO question: Thiopurine (azathioprine or 6-mercaptopurine) vs placebo
P: Patients with Crohn's disease complex perianal fistulae
I: Thiopurine (azathioprine or 6-mercaptopurine)
C: No treatment or placebo

Nr of participants (studies) Follow-up	Quality assessment						Summary of Findings				
							Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Risk with control group	Risk with intervention group		Risk with control group	Risk difference with intervention group
Fistula healing (critical outcome)											
N: 18 (3 studies) 8–24 weeks	Not serious	Not serious	Serious[1]	Very serious[2]	Undetected	Very low	2/7 (28.6%)	6/11 (54.5%)	RR, 2.00 (0.67–5.93)	286 per 1000	286 more per 1000 (from 94 fewer to 714 more)

Reference: Chande N, Townsend CM, Parker CE, et al. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD000545.

Footnotes:
[1] The outcome assessed (fistula improvement or healing) is closely related to, but different from our outcome of interest (fistula healing)
[2] Sparse data (8 events) and wide CI

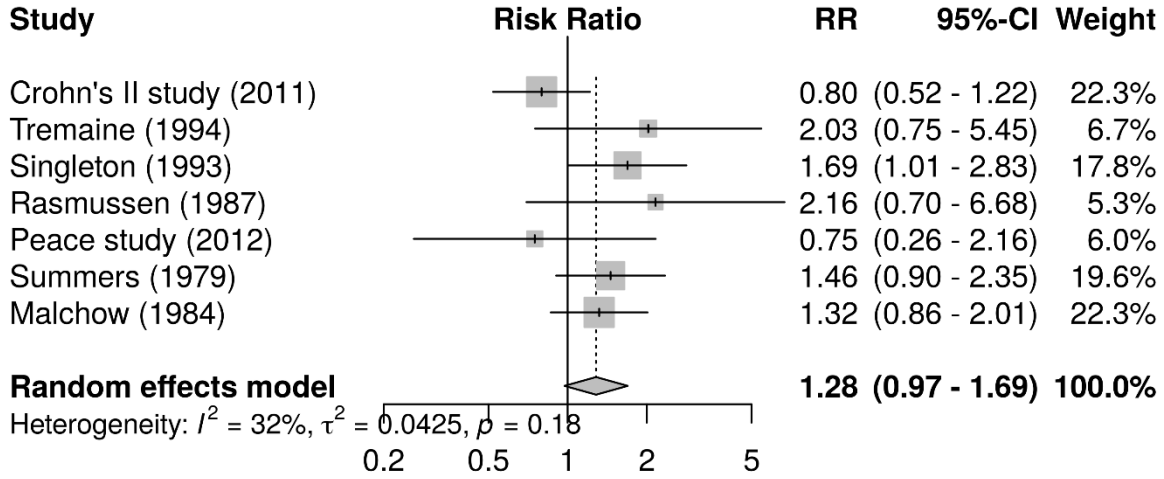
Comment: Evidence was sought also for maintenance of clinical fistula healing, serious adverse events, quality of life, resolution of perianal sepsis, and stoma-free survival; however, data were insufficient.

Abbreviations: RR, risk ratio; CI, confidence interval.

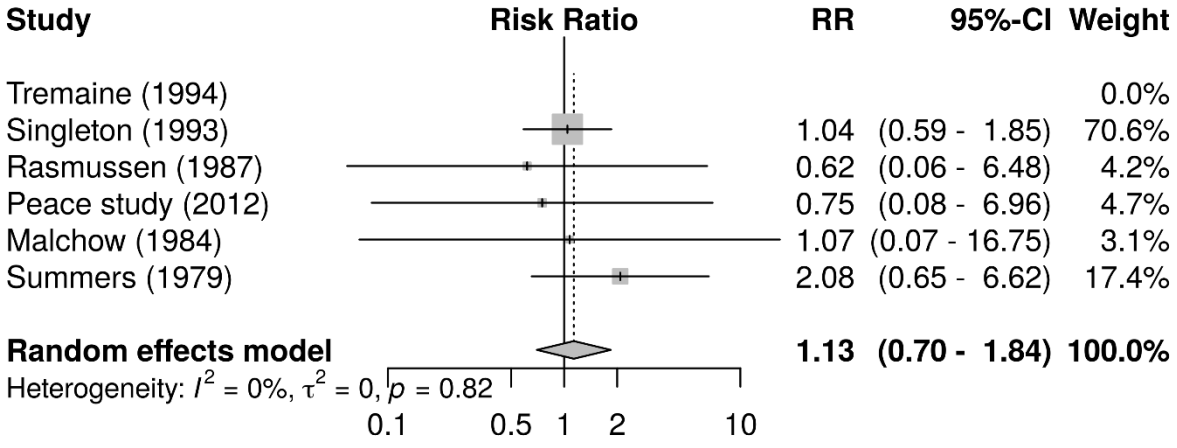
Section 5: Supplementary Figures

When needed, we performed our own meta-analysis, using random-effects analytical techniques. In all forest plots, points on the ***right side*** indicate a ***higher risk of the outcome*** for the intervention, while points on the left side indicate a higher risk of the outcome for the comparator.

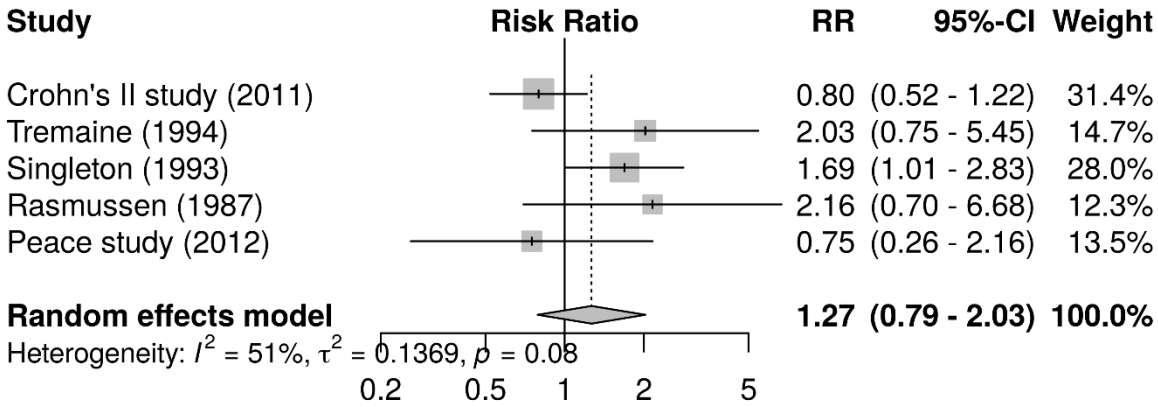
Supplementary Figure 1 - Forest plot: 5-aminosalycilates or sulphasalazine, vs placebo, to induce clinical remission in patients with Crohn's disease



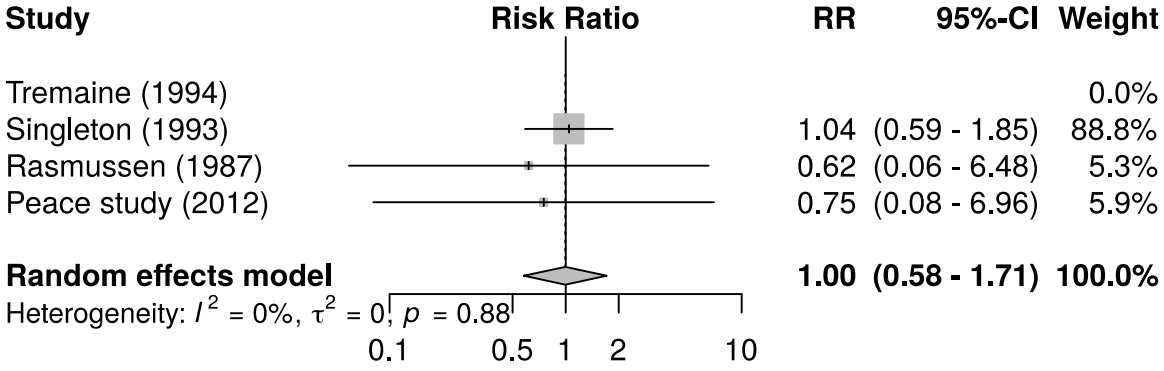
Supplementary Figure 2 - Forest plot: 5-aminosalycilates or sulphasalazine, vs placebo, risk for adverse effects in the treatment of Crohn's disease



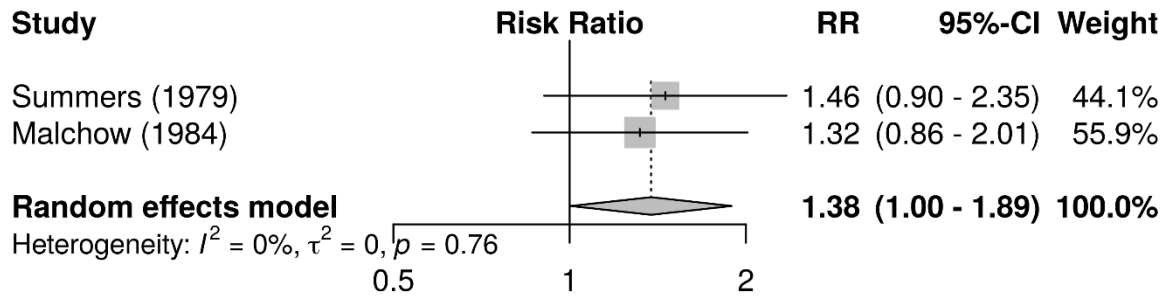
Supplementary Figure 3 – Forest plot: Forest plot: 5-aminosalycilates, vs placebo, to induce clinical remission in patients with Crohn's disease



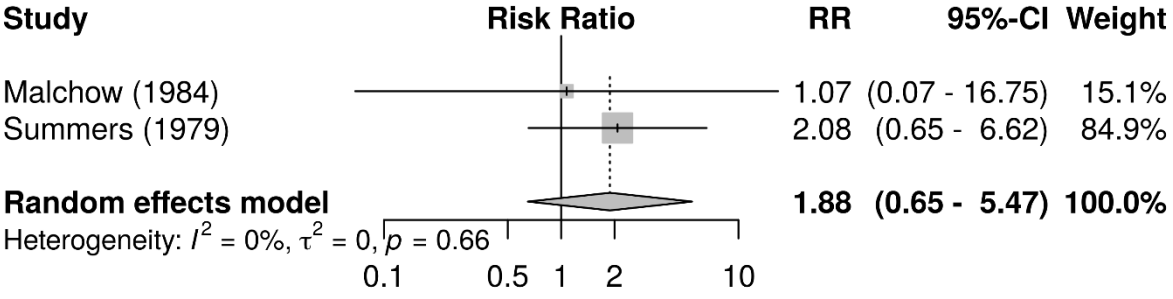
Supplementary Figure 4 – Forest plot: 5-aminosalycilates, vs placebo, risk for adverse effects in the treatment of Crohn's disease



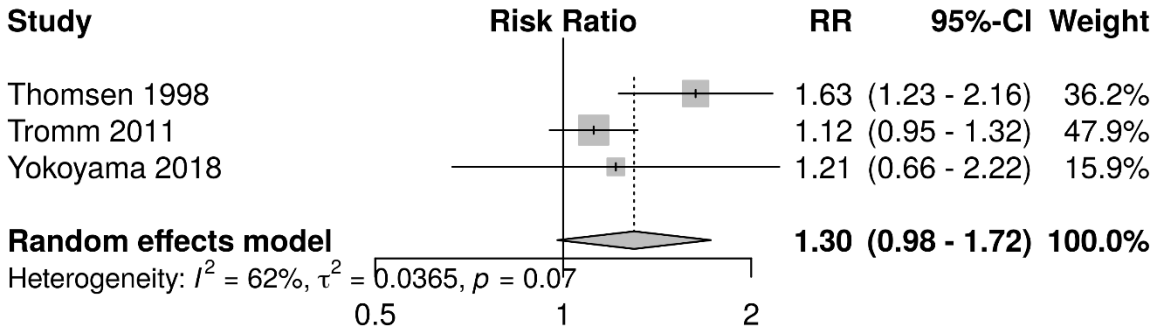
Supplementary Figure 5 – Forest plot: sulphasalazine, vs placebo, to induce clinical remission in patients with Crohn's disease



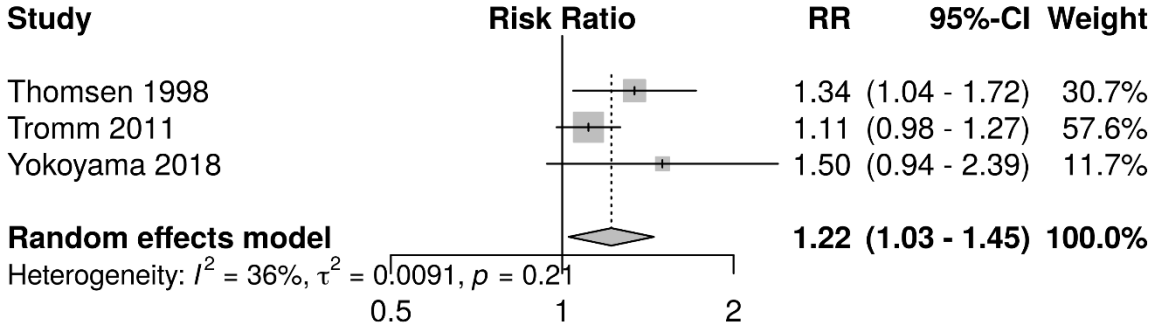
Supplementary Figure 6 – Forest plot: sulphasalazine, vs placebo, risk for adverse effects in the treatment of Crohn's disease



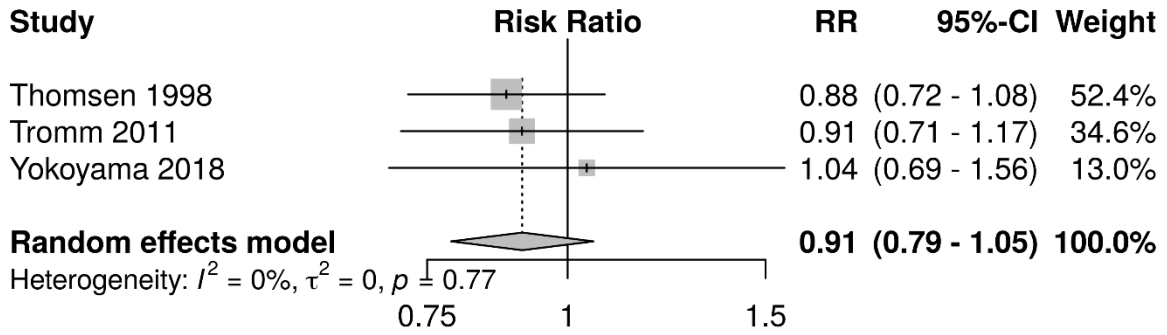
Supplementary Figure 7 - Forest plot: budesonide vs 5-aminosalycilates, to induce clinical remission in patients with Crohn's disease



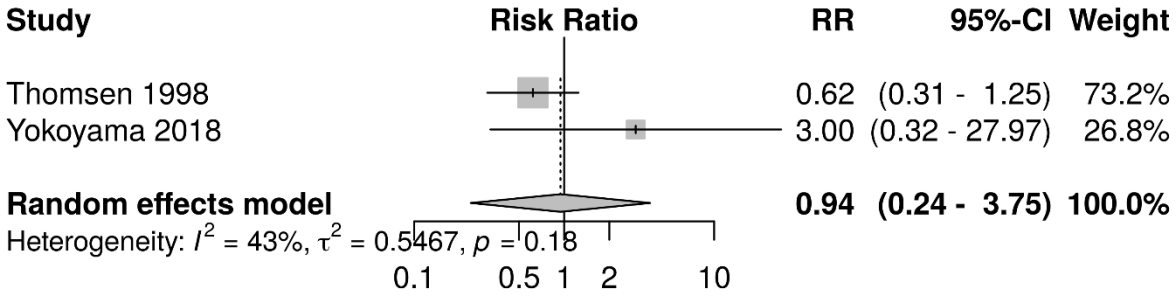
Supplementary Figure 8 - Forest plot: budesonide vs 5-aminosalycilates, to induce clinical response in patients with Crohn's disease



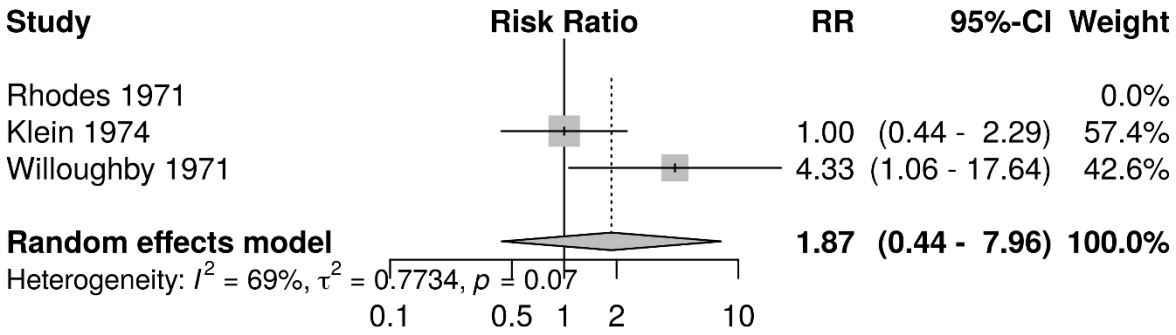
Supplementary Figure 9 - Forest plot: budesonide vs 5-aminosalycilates, risk for adverse effects in the treatment of Crohn's disease



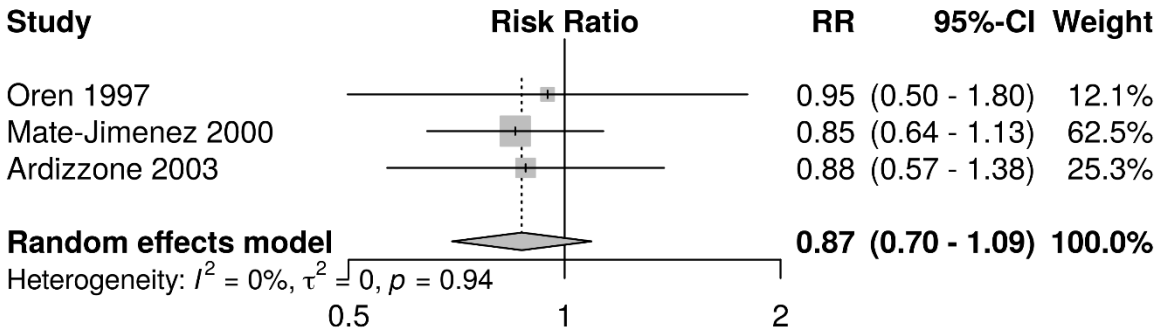
Supplementary Figure 10 - Forest plot: budesonide vs 5-aminosalycilates, risk for serious adverse effects in the treatment of Crohn's disease



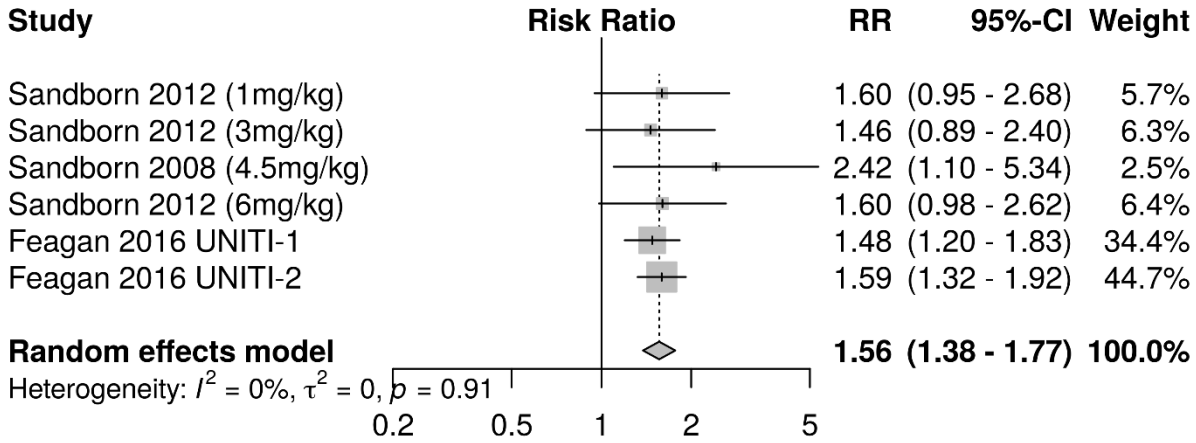
Supplementary Figure 11 - Forest plot: thiopurines vs placebo, to induce clinical remission in patients with Crohn's disease



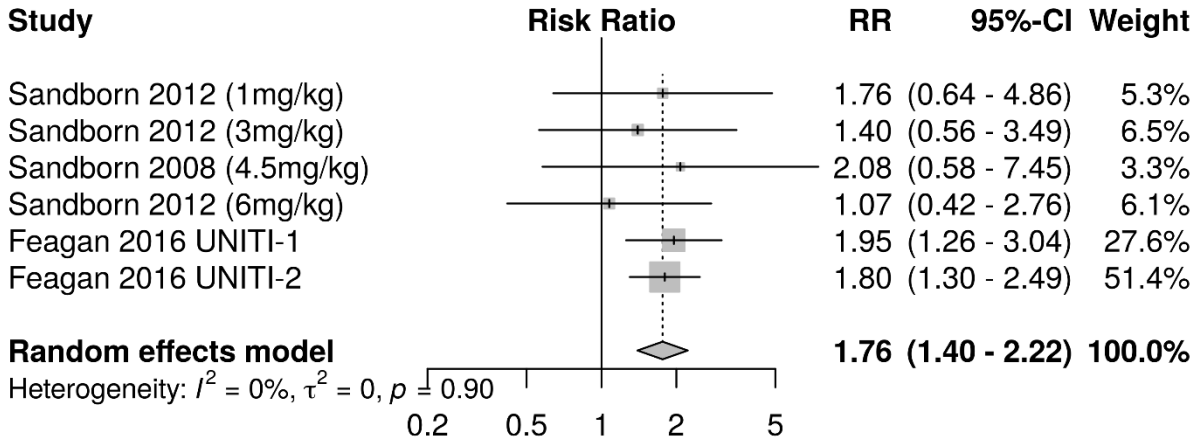
Supplementary Figure 12 - Forest plot reporting clinical remission of methotrexate as compared to thiopurines



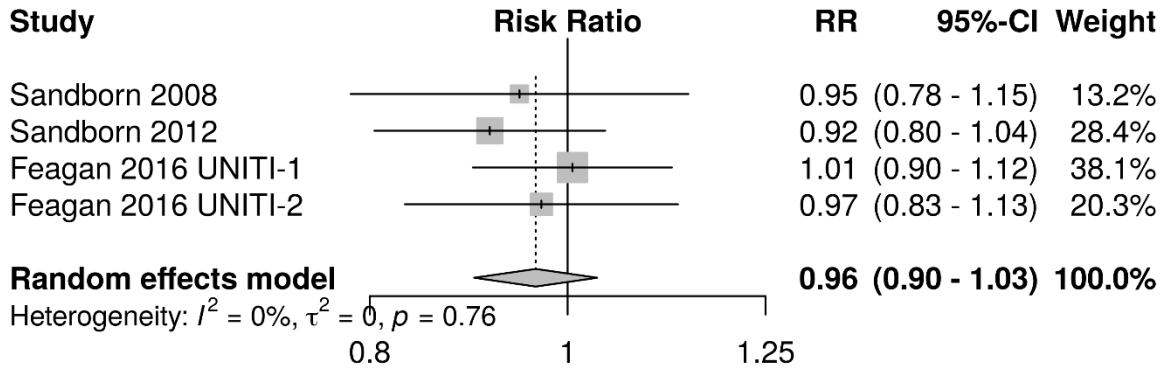
Supplementary Figure 13 - Forest plot: ustekinumab vs placebo, to induce clinical response in patients with Crohn's disease



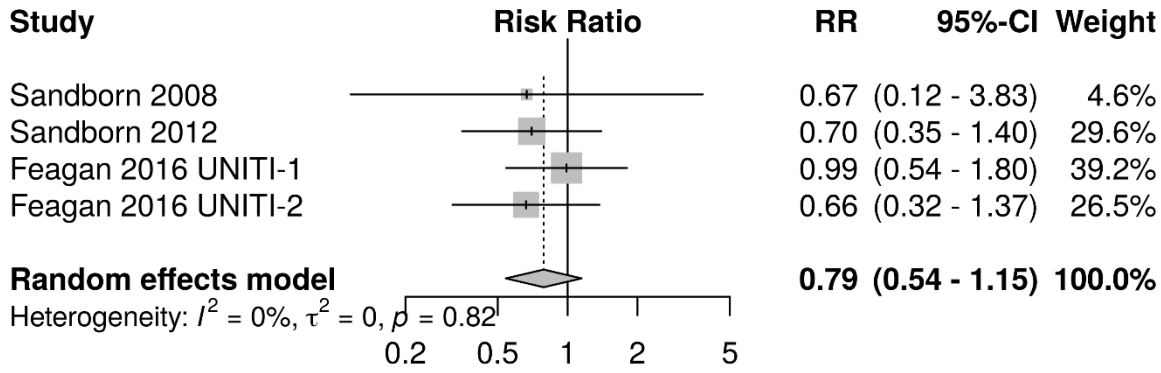
Supplementary Figure 14 - Forest plot: ustekinumab vs placebo, to induce clinical remission in patients with Crohn's disease



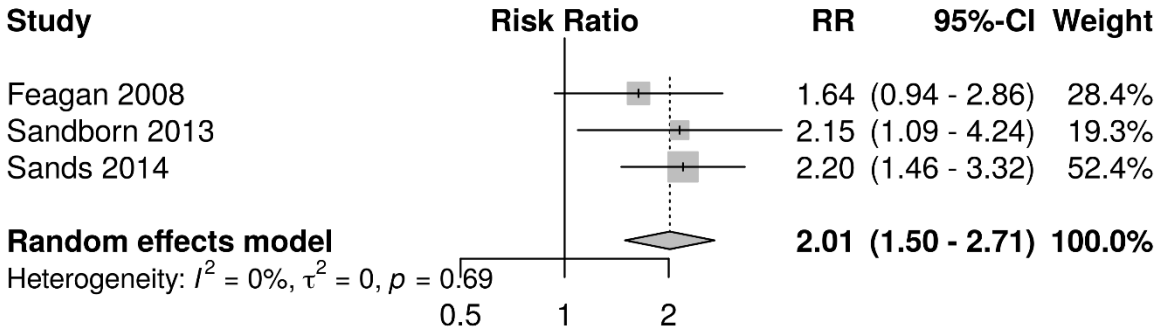
Supplementary Figure 15 - Forest plot: ustekinumab vs placebo, risk for adverse effects in the treatment of Crohn's disease



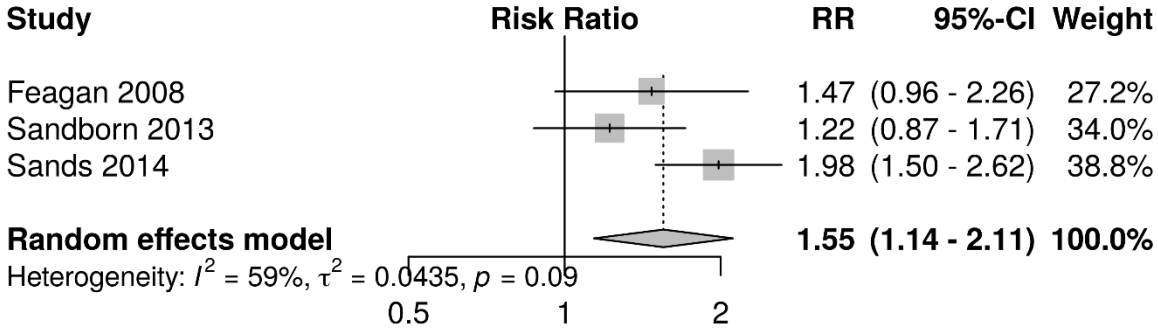
Supplementary Figure 16 - Forest plot: ustekinumab vs placebo, risk for serious adverse effects in the treatment of Crohn's disease



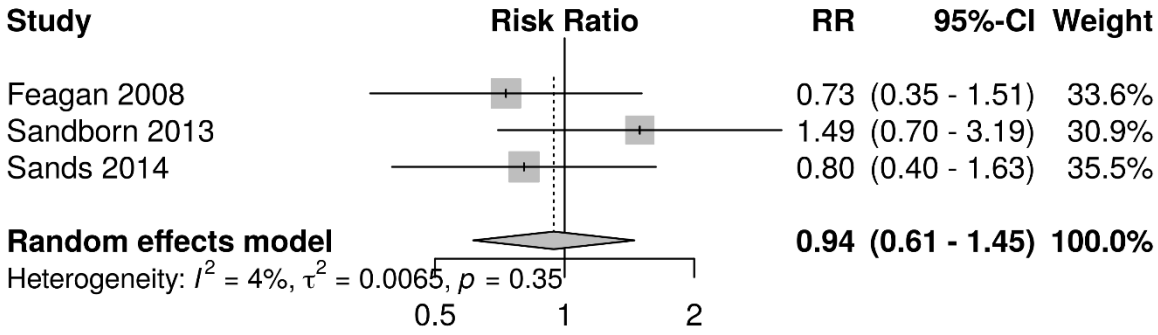
Supplementary Figure 17 - Forest plot: vedolizumab vs placebo, to induce clinical remission in patients with Crohn's disease



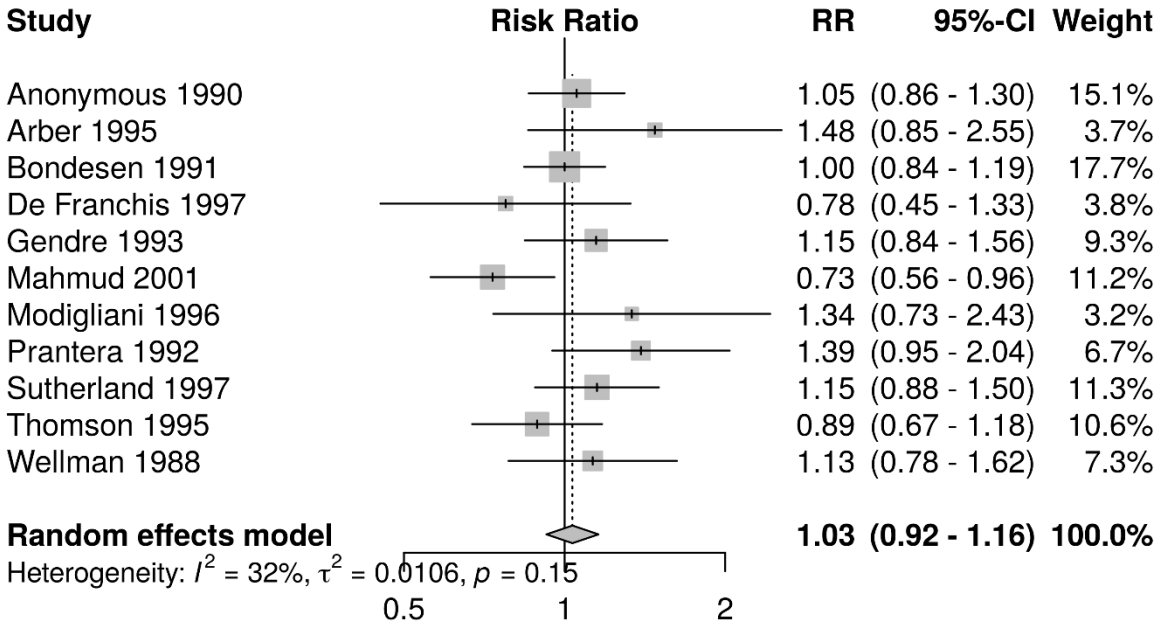
Supplementary Figure 18- Forest plot: vedolizumab vs placebo, to induce clinical response in patients with Crohn's disease



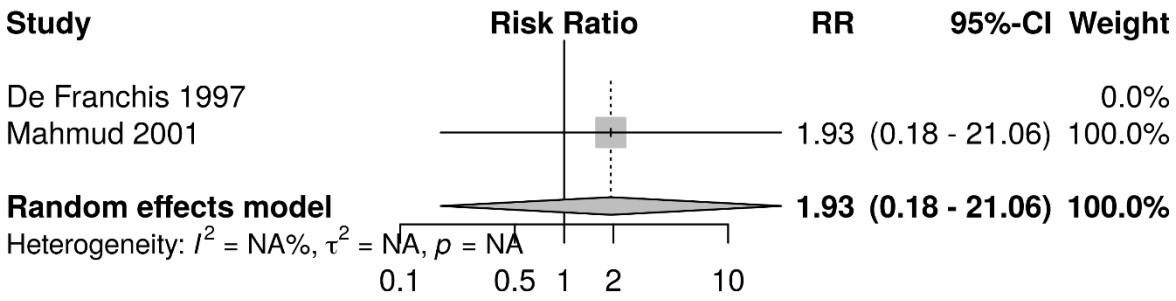
Supplementary Figure 19 - Forest plot: vedolizumab vs placebo, risk for serious adverse effects in the treatment of Crohn's disease



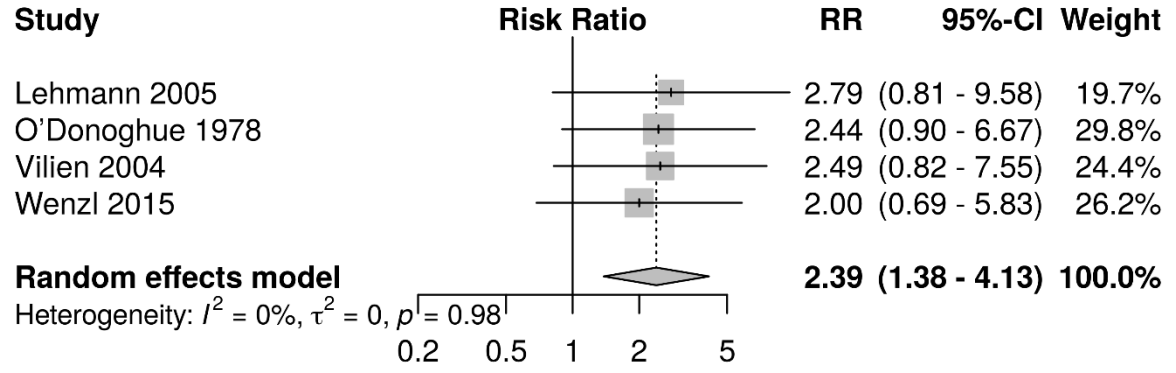
Supplementary Figure 20 - Forest plot: 5-ASA vs placebo, to maintain clinical remission in patients with Crohn's disease



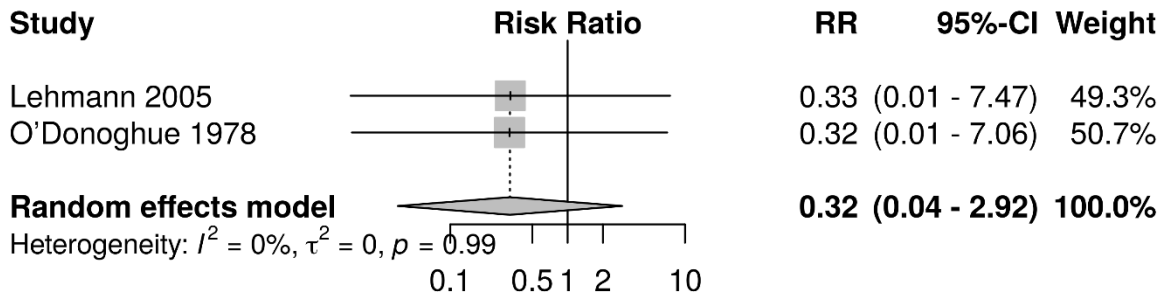
Supplementary Figure 21 - Forest plot: 5-ASA vs placebo, risk for adverse effects during maintenance treatment of Crohn's disease



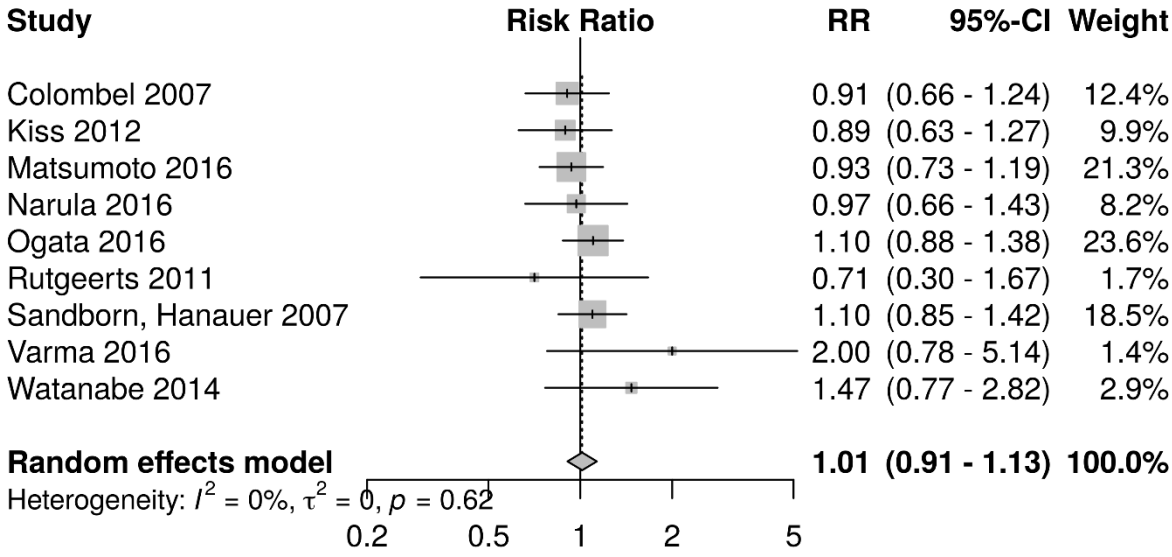
Supplementary Figure 22 - Forest plot: thiopurine discontinuation, vs no discontinuation, risk for relapse in patients with Crohn's disease in clinical remission



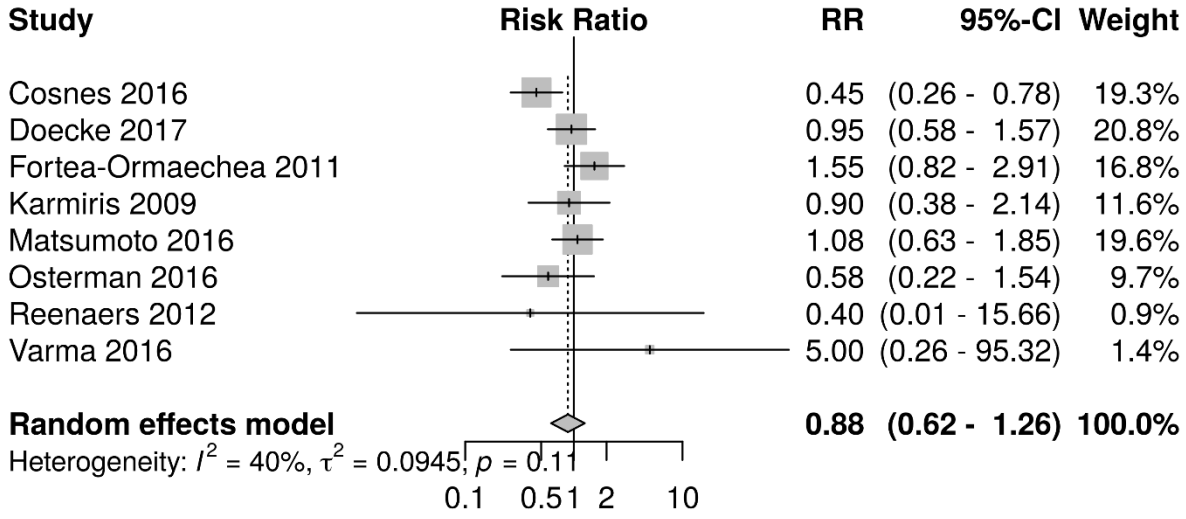
Supplementary Figure 23 - Forest plot: thiopurine discontinuation, vs no discontinuation, risk for serious adverse effects in patients with Crohn's disease in clinical remission



Supplementary Figure 24 - Forest plot: combination treatment with adalimumab and thiopurines, vs treatment with adalimumab only, for maintenance of remission in patients with Crohn's disease



Supplementary Figure 25 - Forest plot: combination treatment with adalimumab and thiopurines, vs treatment with adalimumab only, risk for serious adverse effects in patients with Crohn's disease under treatment for maintenance of remission



Supplementary Figure 26 - Forest plot: infliximab vs placebo, risk for serious adverse effects in patients with Crohn's disease and complex perianal fistulae