NCGC National Clinical Guideline Centre

Crohn's disease

Appendix F

Clinical Guideline <...>

Evidence tables

10 October 2012

NICE's original guidance on Crohn's disease: management in adults, children and young people was published in October 2012; it was partially updated in May 2016 when a new recommendation on inducing remission was added. It has now undergone a further partial update published in May 2019. The full, current recommendations can be found on the NICE website.

This document preserves evidence for areas of the guideline that have not been updated in 2019. Black shading indicates text from 2012 replaced by the 2019 update.

Commissioned by the National Institute for Health and Clinical Excellence

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Contents

1 Evidence tables

1.1 Inducing remission

1.1.1 Conventional glucocorticosteroid for inducing remission

1.1.1.1 Conventional glucocorticosteroid versus placebo or 5-ASA for inducing remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Ref ID: 294 Benchimol et al, 2008[1] Conventional glucocorticosteroid for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews, Issue 2, 2008.	SR: High quality 6 studies included 2 glucocorticosteroid vs. placebo 6 glucocorticosteroid vs. 5-ASA	Total n = 987 Range: 34-452	Inclusion: Active CD, (CDAI > 150 or PCDAI > 15 or HBI or Van Hees Index) in adults and children	Oral or intravenous glucocorticosteroid	Placebo or conventional glucocorticosteroid, 5-ASA or sulfasalazine 2 placebo 1 5-ASA	8 - 24 weeks	1. Induction of remission; CDAI < 150 or PDCDAI < 15 Secondary outcomes: 1. Clinical response (determined by investigator) 2. Mean change in CDAI 3. Adverse events 6. Study withdrawals	See effect size table and GRADE table	Canadian Health Service, Toronto, Canada

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
1o outcome: induction of remission			
Conventional glucocorticosteroid vs. placebo (15 weeks)	2	1.99 (1.51 to 2.64) Favours conventional glucocorticosteroid	NS

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Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Conventional glucocorticosteroid vs. 5-ASA (15 weeks)		3	1.65 (1.33 to2.03) Favours conventional glucocorticosteroid				NS		
2o outcome: Withdrawal from study due to adverse events (15 weeks)									
Conventional glucocorticosteroid vs. placebo (15 weeks)		2	4.57 (0.75 to 27.83)				NS		
Conventional glucocorticosteroid vs. 5-ASA (15 weeks)		6	1.18 (0.61 to 2.29)				NS		
2o outcome: Adverse events									
Conventional glucocorticosteroid vs. placebo (15 weeks)		1	4.89 (1.98 to 12.07)				NS		
Conventional glucocorticosteroid vs. 5-ASA (15 weeks)		5	3.13 (0.99 to 9.90)				Significant heterogeneity (88%)		

1.1.2 Conventional glucocorticosteroid plus 5-ASA versus conventional glucocorticosteroid plus placebo for inducing remission

One additional study was identified[2] which evaluated sulfasalazine as adjunctive therapy. The review of this study has also been included.

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 929 Singleton et al, 1979[2]	RCT	89	Active Crohn's disease: No significant differences with respect to sex, age, severity of illness, distribution of bowel involvement or prior treatment with glucocorticosteroid or sulfasalazine.	Sulfasalazine (1.0 g/15 kg /day+ pred-nisone:0.5-0.75 mg/kg/day	Prednisone + placebo	8 weeks	Change in CDAI	See effect size table and GRADE table	National Cooperative Crohn's Disease Study	

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Inducing remission	1	0.79 (0.58 to 1.07)	NA

In a further study[3] two arms were included in the Cochrane review above[1]. Another arm of this study assessed the use of a combination of sulfasalazine + prednisone. It is possible to analyse this arm of the study in comparison to the prednisone only arm.

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 21 Malchow et al, 1984[3]	Multi-centre RCT; 2 years	452 total 162 previously untreated 292 previously treated	Adults with Crohn's disease of small intestine or colon	Sulfasalazine (3 g/day+ prednisone:48 mg/day and tapering down to 12 mg/day in weeks 6)	Prednisone:48 mg/day and tapering down to 12mg/day in weeks 6 + placebo	6 weeks	Remission (CDAI < 150)	See effect size table and GRADE table	European Cooperative Crohn's Disease Study	

Effect Size			
Outcome	Number of trials	Sulfasalazine + glucocorticosteroid vs. glucocorticosteroid RR (95% CI)	Heterogeneity
Induction of remission	1	0.95 (0.78 to 1.14)	NA

1.1.2.1 Conventional glucocorticosteroid versus azathioprine or mercaptopurine AND conventional glucocorticosteroid plus azathioprine or mercaptopurine versus conventional glucocorticosteroid plus placebo (adjunctive therapy) for inducing remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 2533 Prefontaine et al, 2009[4]	Systematic review; Cochrane Collaboration	447 Range 12-136	Adult patients (age ≥ 18 years) with active CD (CDAI > 150 or Harvey Bradshaw Index >7 or presence of moderate to severe symptoms at the time of entry into the trial) No further data about patient characteristics presented.	Oral AZA (2.0-3.0 mg/kg/d) or MP (50 mg/d or 1.5 mg/kg/d) therapy Patients in 7 studies were being treated with glucocorticosteroid concomitantly. Summers et al 1979 provided the only head-to-head comparisons of glucocorticosteroid, 5-ASA and AZA/MP.	Glucocorticosteroid (Summers 1979) or glucocorticosteroid + placebo (7 studies)	8 weeks to 9 months	Clinical improvement or remission as defined by authors	See effect size table and GRADE table	Canadian Health Service, Toronto, Canada	

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	8	1.57 (1.26 to 1.96)	73%
Induction of remission – AZA/MP as adjunct to glucocorticosteroid	7	1.64 (1.29 to 2.09)	75%
Induction of remission- AZA vs. glucocorticosteroid only (Summers et al 1979)	1	1.57 (0.75 to3.29)	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Glucocorticosteroid-sparing effect, final prednisone dose < 10 mg/day		5	1.81 (1.38 to 2.38)				70%			
Fistula improvement		3	2.00 (0.67 to 5.93)				0%			
Adverse effect		7	2.81 (1.28 to 6.17)				0%			

1.1.2.2 Additional study not included in Cochrane Review: AZA/MP plus glucocorticosteroid versus placebo plus glucocorticosteroid for inducing remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 418 Rosenberg et al, 1975[5] USA	RCT	20	Patients with Crohn's disease of small intestine or small intestine and colon requiring a daily dosage of at least 10mg prednisone for control of symptoms over the 12 weeks prior to entrance into study. Statistical comparison of randomised groups not presented. There were 6 women and 4 men in placebo group and 3 women and 7 men in AZA/MP group. Disease distribution was similar in	AZA/MP tablets 2 mg/kg/day	Glucocorticosteroid (Summers 1979)or glucocorticosteroid + placebo (7 studies)	26 weeks	Mean reduction in glucocorticosteroid dose	See effect size table and GRADE table	GI Research Foundation of Chicago and the L. Sinton Fund	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
			two groups.							

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Mean reduction in glucocorticosteroid dose	1	-15.5mg in AZA group vs. -6.1 in placebo group.	NA

1.1.2.3 Mercaptopurine plus conventional glucocorticosteroid versus placebo plus conventional glucocorticosteroid for inducing remission

Paediatric study not included in Cochrane Review: MP plus conventional glucocorticosteroid vs. placebo plus conventional glucocorticosteroid

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 1595 Markowitz et al, 2000[6] USA	RCT	55 children	Individuals age < 18 years; CD diagnosed within 8 weeks of randomization, disease activity scores (PCDAI and Harvey Bradshaw) in the moderate to severe range. The randomized sample was comparable for age, sex, sites of disease, disease activity and time of enrolment. Mean age 13.2+ 2.4 years	MP tablets, 1.5 mg/kg body weight daily, rounded to 25, 50 or 75 mg doses. All participants received glucocorticosteroid, which were initiated as either 32 mg/day IV methylpredni-sone or 40 mg/day of oral prednisone. Doses were adjusted up or down based on disease activity.	Placebo All participants received glucocorticosteroid, which were initiated as either 32 mg/day IV methylpred-nisone or 40 mg/day of oral prednisone. Doses were adjusted up or down based on disease activity.	18 months	Glucocorticosteroid-sparing; days in remission	See effect size table and GRADE table	Not stated	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments

Outcome	Number of trials	Treatment vs. control	Heterogeneity
Glucocorticosteroid-sparing: Observed to expected ratio of days on prednisone	1	0.73 days in 6 MP group vs. 1.34 days in control group	NA
Remission after one month by Harvey Bradshaw score	1	RR 1.18 (95% CI 0.94-1.47)	

1.1.2.4 Conventional glucocorticosteroid plus methotrexate versus conventional glucocorticosteroid plus placebo (adjunctive therapy) for inducing remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 233 Alfadhli Ahmad et al, 2004[7]	Systematic review; Cochrane Collaboration	5 RCTs; 284 patients 3 RCTs for steroid comparisons; 226 patients	Patients age > 17 years with active CD (CDAI > 150) No further information re patient character-istics provided	Methotrexate parenterally or orally All patients also on prednisone	Placebo All patients also on prednisone	Tapering began after 2-8 weeks and followed up to 9 months	Clinical remission at 16 weeks; withdrawal due to adverse events	See effect size table and GRADE table	Canadian Institute for Health Research	

Outcome	Number of trials	Treatment vs. control	Heterogeneity
Induction of remission at 16 weeks	3	RR 1.25 (0.86 to 1.80)	79%
Withdrawal due to adverse effect	3	RR 6.97 (1.61 to 30.10)	0%

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1818 Feagan et al, 1995[8] Canada	RCT	54	Inclusion: Individuals with chronically active CD with at least three months of symptoms despite daily doses of at least 12.5 mg of prednisone with at least one attempt to discontinue Demographic comparison: The randomized groups were comparable according to age, sex, disease site, CDAI. There were differences in disease duration.	MTX 25 mg/week. The drug was given IV for the first 3 months. Thereafter, patients were switched or oral administration of the same dose. Glucocorticosteroid were administered to all patients. The initial dose was 40 mg daily for 2 weeks, then 30 and 20 mg daily, for the following 2 and 4 weeks. After 8 weeks, if stable, the dose was tapered by 5 mg each week until withdrawal.	Placebo Glucocorticosteroid administered to all patients. The initial dose was 40 mg daily for 2 weeks, then 30 and 20 mg daily, for the following 2 and 4 weeks. After 8 weeks, if stable, the dose was tapered by 5 mg each week until withdrawal.	16 weeks	Induction of remission Withdrawal	See effect size table	Medical Research Council of Canada; Crohn's and Colitis Foundation of America; Davidand MinnieBerk Foundation and Crohn's and Colitis Foundation of Canada	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	37/94 vs. 9/47 RR 2.06 (1.09 to 3.89)	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Withdrawal		1		16/94 vs. 1/47 RR 8.00 (1.09 to 58.51)			NA			

1.1.3 Budesonide for inducing remission

1.1.3.1 Budesonide versus placebo, conventional glucocorticosteroid and 5-ASA for inducing remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Seow et al, 2009[9] ID: 195	SR: High quality 14 studies included 1	Total n = 1420 Range: 18-258	Inclusion: Active CD, (CDAI > 150 or PCDAI > 15 or HBI or Van Hees Index) in adults and children Studies: 2 paediatric, 12 adult	Oral budesonide	Placebo or conventional glucocorticosteroid, 5-ASA or sulfasalazine 11 conventional glucocorticosteroid (prednisolone) 2 placebo 1 5-ASA	8-16 weeks	1. Induction of remission; CDAI < 150 Secondary outcomes: 1. Time to remission 2. Mean change in CDAI 3. Improved quality of life 4. Adverse events 5. Study withdrawals 6. Mortality	See effect size table and GRADE table	Canadian Health Service, Toronto, Canada	

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity	
1^0 outcome: induction of remission				
Budesonide 9 mg vs. placebo (8 weeks)	2	1.96 (1.19 to 3.23) Favours budesonide	NS	
Budesonide 9 mg vs. conventional glucocorticosteroid (eight weeks)	8	0.85 [0.75 to 0.97] Favours conventional glucocorticosteroid	NS	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Budesonide 9 mg vs. conventional glucocorticosteroid (12 weeks)		3	1.02 [0.81 to 1.3] NSD				NS			
Budesonide 9 mg vs. 5-ASA (mesalazine) (8 weeks)		1	1.63 [1.23 to 2.16] Favours budesonide				NA			
Budesonide 9 mg vs. 5-ASA (mesalazine) (12 weeks)		1	1.59 [1.17 to 2.15] Favours budesonide				NA			
2° outcome: Adverse events										
Budesonide 9 mg vs. placebo (eight weeks)		2	0.98 [0.77 to 1.24]				NS			
Budesonide 9 mg vs. conventional glucocorticosteroid (eight weeks)		6	0.64 [0.54 to 0.76]				NS			
2° outcome: Withdrawal from study due to adverse events										
Budesonide 9 mg vs. placebo		2	1.16 [0.45 to 2.99]				NS			
Budesonide 9 mg vs. conventional glucocorticosteroid		5	0.57 [0.18 to 1.84]				NS			
Budesonide 9 mg vs. 5-SA (mesalazine)		2	0.43 [0.18 to 1.02]							
2° outcome: Change in IBDQ score										
Budesonide 9 mg vs. placebo		2	MD 16.79 [-6.34 to 39.91]higher in budesonide group				I^2 = 85%			
2° outcome: Change in CDAI score										
Budesonide 9 mg vs. conventional glucocorticosteroid treatment		6	MD -42.27 [-69.67to -14.86]lower in budesonide group				I^2 = 75%			
Subgroup analysis **Induction of remission in children**										

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
8 weeks (Escher, 2004 and Levine, 2003)										
Budesonide 9 mg vs conventional glucocorticosteroid treatment		2		RR 0.88 (0.58 to 1.33)			NS			
Subgroup analysis **Induction of remission in children 12 weeks**(Escher, 2004 and Levine, 2003)										
Budesonide 9 mg vs conventional glucocorticosteroid treatment		2		RR 0.99 (0.65 to 1.50)			NS			
Subgroup analysis **Change in PCDAI** 10										
Budesonide 9 mg vs conventional glucocorticosteroid treatment		1		MD 4.10 lower (12.77 lower to 4.57 higher)			NA			
Subgroup analysis **Withdrawal due to adverse events** (Escher, 2004)										
Budesonide 9 mg vs conventional glucocorticosteroid treatment		1		RR 0.17 [0.02 to 1.27]			NA			

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Tromm et al, 2010[11] ID: 6433	RCT; multicentre trial conducted in 7 countries	309 patients	Inclusion: Patients aged 18-70 years with active CD (CDAI > 200 and < 400) with CD located in distal ileum and/or ascending colon or distal colon. Demo-graphics similar in all groups	Oral budesonide, either 3mg td or 9mg qd	Mesalazine 1.5 g three times/day	8 weeks	1.Induction of remission; CDAI < 150 2.Mean change in CDAI	See effect size table and GRADE table	Not stated	Study conducted by the International Budenofalk® Study Group

Outcome	Number of trials	Treatment vs. control	Heterogeneity
1° outcome: induction of remission			
Budesonide 9 mg vs. mesalazine 4.5 g/day (8 weeks)	1	107/154 budesonide vs. 95/153 mesalazine RR 1.12 [0.95 to 1.32]	NA
2° outcome: Change in CDAI score			
Budesonide 9 mg vs. mesalazine 4.5 g/day (8 weeks)	1	-149 (91) budesonide vs. -130 (108) mesalazine MD 19 lower [from 41.5 lower to 3.35 higher]	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
2° outcome: Total adverse events										
		1	Budesonide 9 mg vs. mesalazine 4.5 g/day (8 weeks)					NA		
2° outcome: Withdrawal due to adverse events		1	4/154 budesonide vs. 8/153 mesalazine RR 0.50 [0.15 to 1.62]					NA		

1.1.3.2 Budesonide versus conventional glucocorticosteroid for inducing remission in children

See subgroup analysis above in **Table A1.2.1**

1.1.4 5-ASA for induction of remission

1.1.4.1 5-ASAs versus placebo for inducing remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 761 Mahida & Jewell, 1990[12] UK	RCT 6 weeks	40	Inclusion: Adults with active Crohn's disease who did not require glucocorticosteroid Treatment groups matched on sex, age, disease distribution CDAI and lab indicators of inflammation	5-ASA (Pentasa®)	Placebo	6 weeks	Efficacy as determined by fall in Harvey Bradshaw activity score of 2 points or more	See effect size table	Not indicated	

Effect Size			
Outcome	Number of trials	5-ASA vs. placebo RR (95% CI)	Heterogeneity
Induction of remission	1	8/20 (40%) vs. 7/20 (35%) RR 1.14 (0.51 to 2.55)	NA
Total patient withdrawals	1	7/20 vs. 4/20 RR 1.75 (0.61 to 5.05)	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Addi-tional com-ments
Ref ID: 21 Malchow et al, 1984[3] Germany	Multi-centre RCT;	452 total 162 previous-ly untreat-ed 292 previous-ly treated	Adults with Crohn's disease of small intestine or colon. The randomized groups were comparable according to age, sex, duration of disease, CDAI, localisation of disease, body weight, sedimentation rate and previous treatment with sulfasalazine, prednisone, or azathioprine.	6-methylpredniso-lone or Sulfasalazine or Combination: 6-methylpredniso-lone and sulfasalazine	Placebo or 6-methylpredniso-lone or sulfasalazine or Combination: 6-methylpredniso-lone and sulfasalazine	Week 18 for induction; up to 2 years for mainten-ance	Treatment failure or relapse as assessed by CDAI < 150 or change in CDAI, death, pending surgery, new fistula, persistent fever, worsening endoscopic results	See table below	Grants from the Deutsche Forschun gsgeneinschaft	

Effect Size

Outcome	Number of trials	5-ASA vs. placebo RR (95% CI)	Heterogeneity
Induction of remission	1	27/54(50%) vs. 22/58 (38%) RR 1.23 (0.81 to 1.86)	NA
Withdrawal for any reason	1	54/117 vs. 58/110 RR 0.88 (0.67 to 1.14)	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 5 Summers et al, 1979[13] Ref ID: 352 Singleton et al, 1979[14] USA	RCT	295 patients with active disease	Inclusion: Individuals age 15 or greater with Crohn's disease of small intestine or colon Demographic comparison: The randomized groups were comparable according to age, sex, race, duration of disease, CDAI, localisation of disease, body weight, sedimentation rate and previous treatment with sulfasalazine, prednisone, or prior abdominal surgery for CD.	Prednisone or sulfasalazine or azathioprine	Placebo	Part 1 17 weeks to 24 months Part 2 24 months (maintenance)	Remission as measured by CDAI < 150; Adverse events	See effect size table	National Cooperative Crohn's Disease Study: funding source not described	Oral

Effect Size			
Outcome	Number of trials	5-ASA vs. placebo RR (95% CI)	Heterogeneity
Induction of remission	1	28/74 vs. 20/77 RR 1.46 (0.90 to 2.35)	NA
Adverse events	1	10/74 vs. 5/77	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				RR 2.08 (0.75 to 5.80)						
Withdrawal for any reason		1		Reported as an outcome ranking scheme. Not extractable. Raw data not provided.			NA			

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID:2510 Rasmussen et al, 1987[15] Denmark	Multi-centre RCT	67 patients	Inclusion: Adults over 15 years with mild (2-4 motions daily and/or abdominal pain less than daily) to moderate (5 or more motions per day and/or daily abdominal pain) Crohn's disease affecting the small bowel Demographic comparison: The randomized groups were comparable according to age, sex, disease characteristics and severity.	Slow release 5-ASA preparation (Pentasa 250 mg tablets) total dose of 1500 mg delivered in three doses.	Placebo	16 weeks	Improvement as measured by clinical response and CDAI score	See effect size table	Danish Medical Research Council	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	13/30 vs. 9/37 RR 1.78 (0.88 to 3.59)	NA
Adverse events	1	17/30 vs. 23/37 RR 0.91 (0.61 to 1.36)	NA
Withdrawal due to deterioration	1	4/30 vs. 10/37 RR 0.49 (0.17 to 1.42)	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 2204 Singleton et al, 1993[16] and Singleton et al, 1995[17] USA	Multi-centre RCT	310 patients	Inclusion: Adults over 18 years with CD of the small intestine, colon or both and a CDAI 151- 400. Females had either no childbearing potential or were using a medically prescribed form of birth control. Glucocorticosteroid, sulfasalazine or mesalazine were discontinued 7 days before study and immune suppressive drugs were discontinued 90 days before study. Demographic comparison: The randomized groups were comparable according to age, sex, disease location, mean CDAI.	Mesalazine controlled release Pentasa 250 mg tablets Active and placebo tablets identical and administered 4 times a day	Placebo	16 weeks	Induction of remission Withdrawal Quality of Life	See effect size table	Not described	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI) Mean difference	Heterogeneity

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Induction of remission		1		32/75 vs. 14/80 RR 2.44 (1.42 to 4.20) favours 5- ASA			NA			
Withdrawal		1		41/80 placebo 48/80 in 1 g/day group 39/75 in 2 g/day group 26/75 in 4 g/day group 115/230 total withdrawal in all treatment groups RR 2.67 (1.66 to 4.28) significantly higher in 5-ASA 43/230 withdrawal in all groups due to adverse events			NA			
Quality of life		1		Significant QOL improvement ($p < 0.03$) improvements from baseline in all quality-of-life parameters on 4 g/day. No difference on low dose			NA			

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 634 Tremaine et al, 1994[18] USA	RCT	38 patients	Inclusion: 1. Adult patients with CD involving the colon or the colon and distal ileum. 2. CDAI 150 - 450. 3. No more than 20 mg prednisone a day Demographic comparison: The randomized groups were comparable with regard to age, gender, duration of disease and disease characteristics. Patients were randomised within strata by: Disease location Baseline CDAI score Use of glucocorticosteroid	Oral mesalazine (Asacol) in a dose of two tablets (800 mg) four times a day	Placebo	16 weeks	Remission Adverse events	See effect size table	Marion Merrill Dow	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	9/20 vs. 4/18 RR 2.02 (0.75 to 5.46)	NA
Adverse events	1	16/20 vs. 16/18	NA

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				RR 0.90 (0.68 to 1.18)						

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 634 Tremaine et al, 1994[18] USA	RCT	38 patients	Inclusion: 1. Adult patients with CD involving the colon or the colon and distal ileum. 2. CDAI 150 - 450. 3. No more than 20 mg prednisone a day Demographic comparison: The randomized groups were comparable with regard to age, gender, duration of disease and disease characteristics. Patients were randomised within strata by: Disease location Baseline CDAI score Use of glucocorticosteroid	Oral mesalazine (Asacol) in a dose of two tablets (800 mg) four times a day	Placebo	16 weeks	Remission Adverse events	See effect size table	Marion Merrill Dow	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	9/20 vs. 4/18 RR 2.02 (0.75 to 5.46)	NA
Adverse events	1	16/20 vs. 16/18 RR 0.90 (0.68 to 1.18)	NA

1.1.4.2 5-ASA versus placebo for inducing remission – paediatric study

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 668 Griffiths et al, 1993[19] Canada	Randomised, double blind, placebo controlled crossover trial	14 children with one drop out in first 8 weeks	Inclusion: Children ages 5 - 18 years with active CD confined to the small bowel. Activity: Harvey Bradshaw > 4 Demographic comparison: 10 boys, 4 girls with mean age 13.8 + 0.5 (range 9.3 to 16.1)	Oral slow release 5-ASA in 250 mg capsules; dosage of 50 mg/kg/day (max 3 g daily) divided in three doses taken before meals.	Placebo	20 weeks total; 8 weeks, with 4 week washout period and then 8 more weeks of treatment	Induction of remission	See effect size table	Nordic Laboratories, Laval, Quebec Canada	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control Mean difference	Heterogeneity
Induction of remission	1	MD -106.2 (lower) [152 to 60 lower]	NA

1.1.4.3 Sulfasalazine adjunctive therapy for inducing remission

One additional study was identified [2] which evaluated sulfasalazine as adjunctive therapy. The review of this study has also been included.

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Additional comments
Ref ID: 929 Singleton et al, 1979[2]	RCT	89	Active Crohn's disease: No significant differences with respect to sex, age, severity of illness, distribution of bowel involvement or prior treatment with glucocorticosteroid or sulfasalazine.	Sulfasalazine (1.0 g/15 kg /day + pred-nisone: 0.5-0.75 mg/kg/day	Prednisone + placebo	8 weeks	Change in CDAI	See effect size table and GRADE table	National Cooperative Crohn's Disease Study	

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	25/43 5-ASA + glucocorticosteroid vs 34/46 placebo + glucocorticosteroid 0.79 (0.58 to 1.07)	NA

1.1.4.4 5-ASA versus azathioprine/mercaptopurine for inducing remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 5 Summers et al, 1979[13] Ref ID: 352 Singleton et al, 1979[14] USA	RCT		295 patients with active disease	Inclusion: Individuals age 15 or greater with Crohn's disease of small intestine or colon Demographic comparison: The randomized groups were comparable according to age, sex, race, duration of disease, CDAI, localisation of disease, body weight, sedimentation rate and previous treatment with sulfasalazine, prednisone, or prior abdominal surgery for CD.	Prednisone or sulfasalazine or azathioprine	Placebo	Part 1 17 weeks to 24 months Part 2 24 months (maintenance)	Remission as measured by CDAI < 150; Adverse events	See effect size table	National Cooperative Crohn's Disease Study: funding source not described	Oral

Effect Size			
Outcome	Number of trials	5-ASA vs. AZA/MP RR (95% CI)	Heterogeneity

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Induction of remission Summers 1979[14]			1		28/74 vs. 21/59 RR 1.06 (0.68 - 1.67)			NA			
Adverse events Singleton 1979[14]			1		10/74 vs. 19/59 RR 0.42 (0.21 to 0.83)			NA			

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6332 Mate-Jimenez, 2000[20] Spain	RCT		38 patients	Inclusion: Individuals with glucocorticosteroid-dependent CD; age 15 - 70 years Demographic comparison: The randomized groups were comparable according to age, sex, disease extent and smoking. CDAIs varied due to glucocorticosteroid use.	3 g/day 5-ASA	MP 1.5 mg/kg/day	30 weeks	Induction of remission	See effect size table	Not stated	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	1/7 vs. 15/16 RR 0.15 (0.02 to 0.94)	NA

1.1.4.5 5-ASA versus methotrexate for inducing remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6332 Mate-Jimenez, 2000[20] Spain	RCT		38 patients	Inclusion: Individuals with glucocorticosteroid-dependent CD; age 15 - 70 years Demographic comparison: The randomized groups were comparable according to age, sex, disease extent and smoking. CDAI varied due to glucocorticosteroid use.	3 g/day 5-ASA	MP 1.5 mg/kg/day	30 weeks	Induction of remission	See effect size table	Not stated	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	1/7 vs. 12/15 RR 0.18 (0.3 to 1.12)	NA

1.1.5 Azathioprine/mercaptopurine for inducing remission

1.1.5.1 Azathioprine/mercaptopurine versus placebo for inducing remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 5 Summers et al, 1979[13] Ref ID: 352 Singleton et al, 1979[14] USA	RCT		295 patients with active disease	Inclusion: Individuals age 15 or greater with Crohn's disease of small intestine or colon Demographic comparison: The randomized groups were comparable according to age, sex, race, duration of disease, CDAI, localisation of disease, body weight, sedimentation rate and previous treatment with sulfasalazine, prednisone, or prior abdominal surgery for CD.	Prednisone or sulfasalazine or azathioprine	Placebo	Part 1 17 weeks to 24 months Part 2 24 months (maintenance)	Remission as measured by CDAI < 150; Adverse events	See effect size table	National Cooperative Crohn's Disease Study: funding source not described	Oral
Effect Size											

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Outcome		Number of trials	AZA vs. placebo RR (95% CI)					Heterogeneity			
Induction of remission Summers 1979[14]		1	21/59 vs. 20/77 RR 1.37 (0.82 to 2.28)					NA			
Adverse events Singleton 1979[14]		1	19/59 vs. 5/77 RR 4.96 (1.97 to 12.51)					NA			

1.1.6 Economic evidence table TPMT cost effectiveness

A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6 mercaptopurine, Dubinsky, M. C., E. Reyes, and J. et al Ofman, Am J Gastroenterol. 2005 Oct;100(10):2239-47

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: Cost-effectiveness analysis **Study design:** Decision analytic model **Perspective:** US 3rd party payer **Time horizon:** 1 year **Treatment effect duration:** 1 year Discounting: NA	**Population:** Population: Patients with moderate to severe chronically active Crohn's disease (CDAI 150 - 450) **Cohort settings**: Start age = 18 or over **Intervention 1:** Community care[1] **Intervention 2:** TPMT screening[2]	**Total costs (incremental vs CC)[3]:** CC: £4,517* TPMT: £2,442 (-£2,075) * **Currency & cost year:** 2004 US Dollars presented here as 2004 UK pounds **Cost components incorporated**: Drugs, consultations, monitoring, treatment for sepsis and surgery.	**Primary outcome measure:** *Time to response in weeks:* *Mean per patient (incremental vs CC)* CC: 22.41 TPMT: 19.10 (3.31) *Time to sustained response in weeks (per patient)* *Mean per patient (incremental vs CC)* CC: 45.36 TPMT: 42.91 (2.45)	**ICERs** All strategies dominated Community Care CI, Probability cost-effective: NA (PSA not conducted) **Analysis of uncertainty** One way and two way sensitivity analyses were carried out. Parameters varied were drug costs, procedure costs, sepsis probabilities, metabolite level probabilities and dose response probabilities. Probabilities and costs were increased and decreased 50% from the base case and costs of azathioprine were increased 3-fold. The authors state that the cost effectiveness rankings were not affected by the sensitivity analysis; the results were not presented. Probabilistic sensitivity analysis was not conducted.

Data sources & analysis

Approach to analysis: The model was based on a decision tree structure where the differences in costs and outcomes for each strategy were driven by the response to different drug regimens and the number of cases identified with the TPMT strategy. The only adverse event considered was sepsis.

Health outcomes: Clinical inputs were taken from a variety of sources. Of the 15 main efficacy inputs, three were taken from expert opinion, six from randomised trials, three from observational studies, one from a meta-analysis and two from a source where it wasn't clear from the abstract whether or not the trial was randomized. It should also be noted that some of the inputs were taken from a randomised study conducted over 30 years ago, studies in inflammatory bowel disease patients and studies in paediatric Crohn's disease.

Quality-of-life weights: NA

Cost sources: Costs of screening, monitoring and consultation were taken from Current Procedural Terminology (CPT) codes set by the American Medical Association. Drug costs were taken from the Red book 2004 and costs of sepsis and surgery were taken from Cohen 2000, a cost effectiveness analysis of azathioprine in inflammatory bowel disease.

Source of funding: NR; **Limitations**: US perspective, QALYs not used, some aspects of patient pathways and efficacy inputs unclear, no probabilistic sensitivity analysis

A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6 mercaptopurine, Dubinsky, M. C., E. Reyes, and J. et al Ofman, Am J Gastroenterol. 2005 Oct;100(10):2239-47		
Overall applicability*: Partially applicable	**Overall quality**: Potentially serious limitations**	

Abbreviations: CI = confidence interval; ICER = incremental cost-effectiveness ratio; NA = not applicable; ‡ Converted using 2004 Purchasing Power Parities; CC = Community Care; TPMT = Thiopurine Methyltransferase

** Directly applicable/Partially applicable/not applicable; ** Minor limitations/Potentially serious Limitations/Very serious limitations*

1 *Patients receiving 'Community Care' were initially treated with 50 mg AZA. The AZA dose was increased to 100 mg for patients who didn't respond to treatment after three months. Those who didn't respond to 100 mg AZA either underwent surgery (25%) or were given infliximab (75%) as well as continuing on 100 mg AZA. Prednisolone was also co-administered until clinical response was achieved.*

2 *Patients in the TPMT arm were initially given 50 mg AZA, 100 mg AZA or MTX, depending on their TPMT levels. AZA doses could then be increased or decreased according to clinical response, with a minimum of 25 mg and a maximum of 250 mg. Patients not responding to MTX were switched to infliximab; no description was given for patients in this treatment arm not responding to the maximum dose of AZA, though based on the probability inputs quoted, this is likely to be a small number (~3%). Prednisolone was also co-administered until clinical response was achieved.*

3 *Though an incremental analysis was not reported, we conducted an incremental analysis using the costs and effectiveness results quoted in the study. The incremental analysis was conducted in terms of additional weeks of sustained remission.*

1.1.7 Methotrexate for inducing remission

Refer to A .1.1.6 for review of glucocorticosteroid treatment plus methotrexate for inducing remission Alfadhli Ahmad et al, 2004[7] and Feagan et al, 1995[8].

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1887 Oren et al 1997[21] Israel	RCT		23 of 32 in MP group completed; 13 of 26 in MTX group completed and 21of 26 in the placebo group completed	Inclusion: Individuals age 17-75 years with chronic active Crohn's disease with Harvey Bradshaw > 7 Demographic comparison: The randomized groups were comparable according to age, sex, duration of disease, CDAI. There were differences in disease sites between groups.	Methotrexate: 12.5 mg by mouth weekly MP: 50 mg/day by mouth Patients taking 5-ASA or glucocorticosteroid were allowed to continue at the discretion of their physician	Placebo Patients taking 5-ASA or glucocorticosteroid were allowed to continue at the discretion of their physician	9 months	Induction of remission Withdrawal	See effect size table	Crohn's and Colitis Foundation of America	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	10/26 vs. 12/26 RR 0.83 (0.44 to 1.58)	NA
Withdrawal for side effects	1	1/26 vs.0/26 RR 3.00 (0.13 to 7 0.42)	NA

1.1.7.1 Azathioprine/mercaptopurine versus methotrexate for inducing remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 184 Ardizzone et al, 2003[22] Italy	RCT		54 patients	Inclusion: Individuals age 18-75 years with chronic active Crohn's disease (CDAI > 200) with need for glucocorticosteroid therapy > 10 mg/day for at least 4 months, during the 12 months preceding, with at least one attempt to discontinue treatment. Patients had to have been off immunosuppressant drugs for at least 3 months at the time of enrolment in the study. Demographic comparison: The randomized groups were comparable according to age, sex, disease site, CDAI. There were differences in disease duration.	AZA was given orally at a dose of 2 mg/kg per day. Glucocorticosteroid administered to all patients. The initial dose was 40 mg daily for 2 weeks, then 30 and 20 mg daily, for the following 2 and 4 weeks. After 8 weeks, if stable, the dose was tapered by 5 mg each week until withdrawal.	MTX 25 mg/week. The drug was given IV for the first 3 months. Thereafter, patients were switched or oral administration of the same dose. Glucocorticosteroid administered to all patients. The initial dose was 40 mg daily for 2 weeks, then 30 and 20 mg daily, for the following 2 and 4 weeks. After 8 weeks, if stable, the dose was tapered by 5 mg each week until withdrawal.	6 months	Induction of remission Glucocorticosteroid-sparing	See effect size table	Not stated	Oral

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	9/27 vs. 12/27 RR 0.75 (0.38 to 1.48)	NA
Withdrawal	1	3/27 vs. 3/27 RR 1.00 (0.22 to 4.52)	NA

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6332 Mate-Jimenez, 2000[20] Spain	RCT		38 patients	Inclusion: Individuals with glucocorticosteroid-dependent CD; age 15 - 70 years Demographic comparison: The randomized groups were comparable according to age, sex, disease extent and smoking. CDAI varied due to glucocorticosteroid use.	MP 1.5 mg/kg/day	MTX 15 mg/week	30 weeks	Induction of remission	See effect size table	Not stated	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	15/16 vs. 12/15 RR 1.17 (0.88 to 1.56)	NA
Withdrawal	1	1/16 vs. 2/15 RR 0.47 (0.05 to 4.65)	NA

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1887 Oren et al 1997[21] Israel	RCT		23 of 32 in MP group completed; 13 of 26 in MTX group completed and 21of 26 in the placebo group completed	Inclusion: Individuals age 17-75 years with chronic active Crohn's disease with Harvey Bradshaw > 7 Demographic comparison: The randomized groups were comparable according to age, sex, duration of disease, CDAI. There were differences in disease sites between groups.	MP: 50 mg by mouth per day Patients taking 5-ASA or glucocorticosteroid were allowed to continue at the discretion of their physician	Methotrexate: 12.5 mg by mouth weekly Patients taking 5-ASA or glucocorticosteroid were allowed to continue at the discretion of their physician	9 months	Induction of remission Withdrawal	See effect size table	Crohn's and Colitis Foundation of America	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity
Induction of remission	1	13/32 vs. 10/26 RR 1.06 (0.56 to 2.01)	NA
Withdrawal due to AE	1	1/32 vs.1/26 RR 0.81 (0.05 to 12.37)	NA

1.2 Maintaining remission

1.2.1 Conventional glucocorticosteroid for maintaining remission

1.2.1.1 Conventional glucocorticosteroid versus placebo – monotherapy for maintaining remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Ref ID: 5 Summers et al, 1979[13] (treatment results) AND Ref ID: 352 Singleton 1979[14] (adverse events) Country: USA	Multi-centre RCT;		274 patients with quiescent CD (CDAI < 150) Placebo n = 101 6-methylprednisone n = 61 Sulfasal-azine n = 58 Azathioprine n = 54	Inclusion: 274 patients with quiescent CD (CDAI < 150) or those who had surgical removal of disease within one year. All quiescent patients must have had a CDAI > 150 in the previous year. Demographic comparison: The randomized groups were comparable according to age, sex, race, CDAI at time of randomisation, localisation of disease, body weight, prior abdominal surgery.	Prednisone Sulfasalazine Azathioprine	Placebo	2 years	Failure and relapse of patients in remission at entry (CDAI < 150);	See effect size table	Not stated	Oral

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Effect Size											
Outcome			Number of trials	Treatment vs. control			Result				
Failure and relapse of patients in remission at entry (CDAI < 150)			1	Glucocorticosteroid vs. placebo			RR 0.96 (0.48 to 1.91) at one year RR 0.77 (0.38 to 1.58) at two years No significant difference by life table analysis Numerical result not available				
			1	Glucocorticosteroid vs. sulfasalazine			No significant difference by life table analysis Numerical result not available				
			1	Glucocorticosteroid vs. azathioprine			No significant difference by life table analysis Numerical result not available				
Adverse events: Disaster			1	Glucocorticosteroid vs. placebo			RR 3.31 (0.31 to 35.76)				
				Glucocorticosteroid vs. sulfasalazine			RR 4.76 (0.23 to 97.05)				
				Glucocorticosteroid vs. azathioprine			RR 0.89 (0.13 to 6.07)				
Adverse events: Severe			1	Glucocorticosteroid vs. placebo			RR 3.55 (1.53 to 8.21)				
				Glucocorticosteroid vs. sulfasalazine			RR 7.13 (1.70 to 29.83)				
				Glucocorticosteroid vs. azathioprine			1.66 (0.76 to 3.61)				

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Ref ID: 60 Smith et al, 1978[23] Country: UK; Wales	RCT		59 patient who were symptom free and had no clinical indicatio n for glucocort icosteroi d treatmen t	Inclusion: 59 patients in three groups: Group I had bowel resected and had no obvious residual disease; 2. Group II had also had recent surgery but there was residual disease; Group III were known to have active CD but had no Demographic comparison: The randomized groups were comparable according to age, sex, disease duration and localisation of disease	Prednisone	Placebo	3 years	Clinical Relapse , i.e. when patients required additional prednisone to control recurrent or persistent abdominal symptoms	See effect size table	Donation of placebo tablet from Roussel Labora-tory	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control	Result
Relapse	1	Glucocorticosteroid vs. placebo	RR 5.73 (0.31 to 106.11) at one year RR 1.20 (0.37 to 3.94) at two years No significant difference by life table analysis
Withdrawal due to clinical relapse after 3 years	1	Glucocorticosteroid vs. placebo	RR 1.05 (0.42 to 2.65)

1.2.1.2 Conventional glucocorticosteroid versus placebo – combination therapy (CC + 5-ASA versus placebo) for maintaining remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Ref ID: 21 Malchow et al, 1984[3] Country: Germany	Multi-centre RCT;		237 patients with quiescent CD (CDAI < 150) Placebo n = 52 6-methylprednisone n = 66 Sulfasal-azine n = 63 Combina-tion of 6-methylprednisone and sulfasal-azine n = 56	Inclusion: 237 patients with quiescent CD (CDAI < 150) Demographic comparison: The randomized groups were comparable according to age, sex, duration of disease, CDAI, localisation of disease, body weight, sedimentation rate and previous treatment with sulfasalazine, prednisone, or azathioprine.	6-methylpredni-solone Sulfasalazine Combination: 6-methylprednisolone and sulfasalazine	Placebo OR 6-methylpredni-solone OR Sulfasalazine OR Combination: 6-methylprednisolone and sulfasalazine	2 years	Failure and relapse of patients in remission at entry (CDAI < 150); Worsening of disease; Adverse events	See effect size table	Not stated	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control	Result
Failure and relapse of patients in remission at entry (CDAI < 150)	1	Glucocorticosteroid vs. placebo	RR 0.76 (0.50 to 1.14) at one year RR 0.82 (0.56 to 1.19) at two years

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
			1	Glucocorticosteroid + sulfasalazine vs. placebo				No significant difference by life table analysis Numerical result not available			
			1	Glucocorticosteroid vs. sulfasalazine				No significant difference by life table analysis Numerical result not available			
Withdrawal due to side effects of drugs			1	Glucocorticosteroid vs. placebo				RR 0.16 (0.01 to 3.23)			
			1	Glucocorticosteroid + sulfasalazine vs. placebo				RR 0.46 (0.04 to 4.97)			
			1	Glucocorticosteroid vs. sulfasalazine				RR 0.19 (0.01 to 3.90)			

1.2.2 5-aminosalicylate for maintaining remission

1.2.2.1 5-aminosalicylate versus placebo for maintaining remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 2112 Arber et al, 1995[24] Country: Israel	RCT		59	Inclusion: Patients in remission for at least six months with Harvey Bradshaw Index score < 4. Demographic comparison: There were no significant differences between groups in age, sex, duration of remission, disease activity score, disease location, smoking or laboratory parameters	Mesalazine 250 mg four times a day	Placebo	12 months	A rise of more than 4 points in the Harvey Bradshaw Index	See effect size table	Rafa Laboratories for supply of tablets	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control 5-ASA vs. placebo	Result RR (95% CI)
Relapse	1	6/28 (55 %) vs. 15/31(27%)	0.44 [0.20 to 0.98]
Relapse + withdrawals* *Ten patients were withdrawn from the trial, four from the placebo group and six from the treatment group. Five were withdrawn because of noncompliance,	1	12/28 vs. 19/31* *Agrees with Cochrane numbers and with Ford et al	0.70 [0.42 to 1.17]

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
three patients were lost to follow-up and one in each group had side effects (headache)											
Withdrawal due to adverse events			1	1/28 vs. 1/31				1.11 [0.07 to 16.88]			

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6307 Gendre et al, 1993[25] Country: France	RCT		161	Inclusion: Patients older than 15 years; Clinically quiescent disease (CDAI < 150); no glucocorticosteroid or immunosuppressive therapy for at least 1 month before entry into the trial; clinical remission of less than 24 months duration Demographic comparison: No significant differences in age, sex, previous surgery, disease location, CDAI at trial onset, lab	Mesalazine (Pentasa)	Placebo	2 years	Clinical relapse (either CDAI of > 250 or a CDAI between 150 and 250 but over the baseline value by > 50 points, with confirmation 2 weeks later) OR Surgery for an acute complication	See effect size table	Institut National de la Sante et de la Recherche Medical	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control Mesalazine vs. Placebo	Results RR (95% CI)
Relapse (medical and surgical)	1	30/80 vs. 36/81	0.84 [0.58 to 1.23]
Relapse + withdrawals Table two presents 'Withdrawals without relapse or acute complications.' 17 patients were withdrawn for side effects; 25 were withdrawn for other reasons: 5 for non-compliance; 6 for loss to follow- up; 55 for intention to become pregnant; 9 for personal reasons. This total of 23 patients		53/80 vs. 55/81* *Cochrane review numbers are as follows: 54/80 vs. 55/81 Study data does not account for the one additional patient included in the Cochrane review mesalazine numerator. Agrees with Ford et al	0.96 [0.78 to 1.19]

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
in the mesalazine group and 19 patients in the placebo group were listed as 'withdrawals without relapse.'											
Withdrawal due to adverse events			1		7/80 vs. 10/81			0.71 [0.28 to 1.77]			

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6305 International Mesalazine Study Group[26] Country: Belgium, Canada, France, Italy, South Africa, Spain, Sweden, UK	RCT		206	Inclusion: Patients with CDAI < 150 whose disease must have been controlled for the preceding month on no glucocorticosteroid or stable low dose prednisone 2.5 mg/day or less. Demographic comparison: No significant differences in sex, age, weight, duration of disease or time in remission.	5-ASA	Placebo	12 months	CDAI > 150 which had increased 60 points from the pre-trial index	See effect size table	Smith Kline & French	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control Mesalazine vs. placebo	Results RR (95% CI)
Clinical relapse	1	29/125 (23%) vs. 44/123 (36%)	0.65 [0.44 to 0.96]
Relapse + withdrawal Exclusions from analysis and withdrawals: default (4); entry violations (21); non-compliance (16); patient request (1); withdrawal due to adverse events (13).	1	61/125 vs. 67/123* *Cochrane numbers are as follows: 49/125 vs. 52/123 Not able to identify basis for these numerators. Ford et al numerators appears to exclude withdrawals due to adverse events: 53/125 vs. 62/123	0.90 [0.70 to 1.14]
Withdrawal due to adverse events	1	8/125 vs. 5/123	0.65 [0.44 to 0.96]

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6308 Mahmud 2001[27] Country: Ireland , UK & France	RCT		328	Inclusion: 18 years or over; in remission for at least one month prior to randomisation. Remission defined as CDAI < 150 and clinical assessment by investigator Demographic comparison: There were no significant differences in age, gender, weigh, months in remission (mean 21.97 [1.97] and 20.91 [2.0]) and disease location	5-ASA (Olsalazine)	Placebo	52 weeks	Relapse by CDAI < 150 or by clinical assessment	See effect size table	Pharmacia Upjohn	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control Olsalazine vs. placebo	Results RR (95% CI)
Relapse (CDAI and clinical)	1	55/167 vs. 59/161	0.90 [0.67 to 1.21]
Relapse + withdrawal Reasons for study termination other than relapse by CDAI or by clinical symptoms: Serious adverse events (3); intolerable adverse events (43); disallowed concomitant medication (6); patient consent withdrawn (9); other protocol violation (7); other (3); unknown (1).	1	110/167 vs. 86/161* *Agrees with Cochrane and Ford et al	1.23 [1.03 to 1.48]
Withdrawal due to adverse events	1	35/167 vs. 11/161	4.82 [2.62 to 8.87]

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6309 Prantera 1992[28] Country: Italy	RCT		125	Inclusion: Age between 18 and 65 years; in remission for at least 3 months but not > 2 years with CDAI < 150; no glucocorticosteroid, sulfasalazine or metronidazole for at least 3 months or azathioprine for at least 6 months. Demographic comparison: There was no significant difference in pre-trial characteristics including age, gender, duration of disease, duration of remission, disease location.	5-ASA (Asacol)	Placebo	12 months	Clinical relapse defined as CDAI > 150 with an increase of 100 points over the baseline value, confirmed at a second visit 1 week later.	See effect size table	Braco and Giuliani Societa per Aziomi	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control Asacol vs. placebo	Results RR (95% CI)
Clinical relapse	1	19/64 vs. 32/61	0.57 [0.36 to 0.88]
Clinical relapse + withdrawals Withdrawals listed in Table 2: entry violation (2); adverse events (8); Lost to follow-up (1); intercurrent illness (2) and request to stop (2).	1	29/64 vs. 37/61* Agrees with Cochrane review and Ford et al	0.75 [0.53 to 1.05]
Withdrawal due to adverse events	1	5/64 vs. 3/61	1.59 [0.40 to 6.36]

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Ref ID: 5 Summers et al, 1979[13] (treatment results) AND Ref ID: 352 Singleton 1979[14] (adverse events) Country: USA	Multi-centre RCT;		274 patients with quiescent CD (CDAI < 150) in total sample of four treatment arms Placebo n = 101 Sulfasal-azine n = 58	Inclusion: Patients with quiescent CD (CDAI < 150) or those who had surgical removal of disease within one year. All quiescent patients must have had a CDAI > 150 in the previous year. Demographic comparison: The randomized groups were comparable according to age, sex, race, CDAI at time of randomisation, localisation of disease, body weight, prior abdominal surgery.	Sulfasalazine	Placebo	2 years	Failure and relapse of patients in remission at entry (CDAI < 150)	See effect size table	Not stated	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control Sulfasalazine vs. placebo	Result
Maintenance of remission	1	36/58 vs. 65/101 12/39 vs. 23/57	RR 0.96 [0.75 to 1.24] at one year RR 0.76 [0.43 to 1.34] at two years
Adverse events: Disaster	1	0/58 vs. 1/101	RR 0.58 [0.02 to 13.92]

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Adverse events: Severe			1	2/58 vs. 7/101				RR 0.50 [0.11 to 2.32]			

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1013 Thomson 1995[29] Country: Canada	RCT		286	Inclusion: Ages 18-70 with CDAI < 150 with one period of clinical activity (CDAI > 150) within 18 months. None of the patients used glucocorticosteroid or immunosuppressants during the trial Demographic comparison: The treatment groups were comparable with respect to age, gender, height and weight, disease site, length of time in remission.	5-ASA (Claversal/Mesasal: tables with an acrylic based resin coating which is specifically designed to release the active component [5-ASA] in the distal ileum and colon).	Placebo	12 months	Relapse defined as CDAI > 150 with at least a 60 point increase from the baseline index score.	See effect size table	SmithKline Beecham	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control Claversall/Mesasal vs. placebo	Results RR (95% CI)
Clinical relapse	1	33/138 vs. 38/148	0.93 [0.62 to 1.40]
Relapse + withdrawal Patients were withdrawn prematurely (before 12 months) due to the following reasons: CDAI > 150 that increased 60 points from baseline (definition of relapse); any adverse event where continuation of the drug would be inappropriate; a disease state requiring therapy prohibited by the protocol; non compliance with the study medication; pregnancy and patient initiated requests to withdraw for any		85/138 vs. 84/148* *Agrees with Cochrane and Ford et al	

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
reason.											
Withdrawal due to adverse events			1	29/138 vs. 29/148				1.07 [0.68 to 1.70]			

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID 2278 Wellman, 1988[30] Country: West Germany	RCT		66	Inclusion: Patients in remission with CDAI below 120 for 3 months without glucocorticosteroid. Demographic comparison: There were no significant differences between study groups on admission to trial (details not provided).	5-ASA (Mesalazine)	Placebo	1 year	Relapse defined as CDAI > 150	See effect size table	Not stated	Oral

Effect Size			
Outcome	Number of trials	Treatment vs. control Mesalazine vs. placebo	Results RR (95% CI)
Relapse (no withdrawals reported)	1	10/31 vs. 14/35* Study not included or excluded in Cochrane review Agrees with Ford et al	0.81 [0.42 to 1.55]

1.2.2.2 Economic evidence tables – mesalazine for maintaining remission

Drug treatments for maintaining remission in Crohn's disease: A lifetime cost-utility analysis, Trallori, G.; Messori, A., Pharmacoeconomics, 1997 11(5): 444-453				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Not clearly stated/described **Approach to analysis:** As above **Perspective:** Healthcare payer perspective **Time horizon:** Lifetime **Treatment effect duration:** Short-term efficacy based on 2 years of data from clinical trials; long-term efficacy based on historical data on frequencies of "events" associated with Crohn's disease **Discounting:** Costs: 5%; Outcomes: 5%	**Population:** Patients with inactive Crohn's disease **Cohort settings:** Start age = NR Male/Female = NR **Intervention 1:** Mesalazine **Intervention 2:** No maintenance treatment	**Total costs (mean per patient):** Mesalazine: $50,779 (£32,367) No maintenance therapy: $49,826 (£31,760) Incremental: $953 (£607) (CI , ; p=NR) **Currency & cost year:** (e.g. 1994 US dollars (presented here as 1994 UK pounds‡) **Cost components incorporated:** Cost of relapses, hospitalisation, surgical interventions and drug therapy	**Primary outcome measure:** QALYs (mean per patient) Mesalazine: 17.14 QALYs No maintenance therapy: 16.95 QALYs Incremental: 0.19 (CI , ; p=NR) **Other outcome measures (mean):** None reported	**Primary ICER (Mesalazine vs no maintenance therapy):** ICER: $5,015 (£3197) per QALY gained (d/a) CI: N/A Probability cost-effective: N/A **Subgroup analyses:** N/A **Analysis of uncertainty:** Two one-way sensitivity analyses conducted. One for assessing the effect of varying HRQoL scores (for remissions in operated patients) and the other for +/- 20% of the cost of illness. Varying HRQoL scores did not have significant impacts on the economic results. A 20% decrease in cost of illness (relapses, hospitalisation and surgical interventions), increase the ICER to $26,436 (£16,853) per QALY gained. A 20% increase in cost of illness, however, gave an ICER of -$16,406 (£10,458) per QALY gained.
Data sources				
Health outcomes: Short-term efficacy data were synthesized from a meta-analysis of 4 controlled trials (Caprilli et al. 1992; Gendre et al. 1993; IMSG 1990; Prantera et al. 1992) with long-term efficacy data based on a large-scale survey of the 583 patients that enrolled in the clinical trials meta-analyzed (Pera and Rocca, 1995). **Quality-of-life weights:** Quality of life scores determined by a group of 10 gastroenterologists as part of the study. **Cost sources:** Costs of illness derived from the UK healthcare system and mesalazine costs are those applicable in the UK in 1994.				
Comments				
Source of funding: NR; **Limitations:** The choice of model (and its structural elements) is not clearly described. No probabilistic sensitivity analysis was conducted.				
Overall applicability*: Partially applicable **Overall quality**: Potentially serious limitations**				

*Abbreviations: CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 1994 Purchasing Power Parities [http://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP] * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

1.2.2.3 5-aminosalicylates versus azathioprine for maintaining remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Ref ID: 5 Summers et al, 1979[13] (treatment results) AND Ref ID: 352 Singleton 1979[14] (adverse events) Country: USA	Multi-centre RCT;		274 patients with quiescent CD (CDAI < 150) in total sample of four treatment arms Placebo n = 101 Sulfasal-azine n = 58	Inclusion: Patients with quiescent CD (CDAI < 150) or those who had surgical removal of disease within one year. All quiescent patients must have had a CDAI > 150 in the previous year. Demographic comparison: The randomized groups were comparable according to age, sex, race, CDAI at time of randomisation, localisation of disease, body weight, prior abdominal surgery.	Sulfasalazine	Azathioprine	2 years	Failure and relapse of patients in remission at entry (CDAI < 150)	See effect size table	Not stated	Oral

Effect Size

Outcome	Number of trials	Treatment vs. control Sulfasalazine vs. azathioprine	Result
Maintaining remission	1	43/58 vs. 46/54 31/58 vs. 29/54	RR 0.87 (0.72 to 1.05) at one year RR 1.00 (0.70 to 1.41) at two years
Adverse events: Disaster	1	0/58 vs. 2/54	RR 0.19 (0.01 to 3.80)

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administra-tion
Adverse events: Severe			1	2/58 vs. 8/54				RR 0.23 (0.05 to 1.05)			

1.2.3 Budesonide for maintaining remission

1.2.3.1 Budesonide versus placebo for maintaining remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 1814 Ferguson et al, 1998[31] Country: Multicentre trial in twenty centres from seven European countries (including UK) and Australia.	RCT	75 patients	Inclusion: Ages 18-65 years with established diagnosis of CD limited to the ileal or ileocaecal region and/or ascending colon; had completed the 12 week trial of therapy in acute CD; were in clinical remission with CDAI < 150. Demographic comparison: Three study groups were similar in the majority of characteristics, except for a low initial CDAI in the 3mg group and for a low proportion of patients with a previous resection in the 6mg group. However, these factors were	Patients were randomised to one of two intervention arms: Budesonide 6 mg or Budesonide 3 mg daily	Placebo	1 year	CDAI > 150 together with an increase of at least 60 units from entry or withdrawal due to clinical deterioration; suppressed adrenal function as measured by cortisol levels before and after ACTH stimulation	See effect size table	Astra Draco AB, Sweden	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			found not to have any significant influence on the comparison between the treatments.								

Effect Size

Outcome	Number of trials	Treatment vs. control	RR (95% CI)
Relapse at 1 year – therapeutic failure only	1	Budesonide 6 mg:10/22 vs. 14/27 Budesonide 3 mg: 11/26 vs. 14/27	0.88 (0.49 to 1.57) 0.82 (0.46 to 1.45)
Relapse at 1 year (therapeutic failure) plus withdrawals including unintended pregnancy, non-compliance, duodenal ulcer and visual impairment	1	Budesonide 6 mg:13/22 vs. 14/27 Budesonide 3 mg: 12/26 vs. 14/27 Unable to reconcile Cochrane data. Ford et al combines doses. Total numbers agree except placebo patient who withdrew due to improvement is included in Ford data.	1.14 (0.69 to 1.88) 0.89 (0.51 to 1.55)
Adverse events – suppressed adrenal function (Baseline variable - failure to have a cortisol increase of at least 200 nmol/litre)	1	Budesonide 6mg:3/17 vs. 3/18 Budesonide 3mg: 2/19 vs. 3/18 Unable to reconcile 3 mg Cochrane data	1.06 (0.25 to 4.45) 0.63 (0.12 to 3.35)
Withdrawal due to adverse events	1	Budesonide 6 mg:1/22 vs. 0/27 Budesonide 3 mg: 1/26 vs. 0/27	3.65 (0.16 to 85.46) 3.11 (0.13 to 73.09)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 1844 Greenberg et al, 1996[32] Country: Canada	RCT	105 patients in 23 Canadian centres	Inclusion: Older than 18 years and previously participated in an 8 week placebo-controlled trial that evaluated the efficacy of budesonide for active ileocaecal CD. Patients entered in symptomatic remission as defined by CDAI < 150. Demographic comparison: Baseline characteristics including gender, age, weight, disease site, prior resections, duration of disease, prior treatments, IBDQ score and CDAI were similar in all	3 mg budesonide Or 6 mg budesonide administered once daily	Placebo	1 year	Relapse, defined as CDAI > 150 together with an increase of at least 60 points or patients who were withdrawn from the study and who required medical or surgical treatment. Changes in quality of life were assessed with IBDQ	See table below	In collaboration with Astra Draco AB, Lund, Sweden	Oral	Sample size estimation: 90 patients to detect a 40% absolute difference in proportion of patients maintaining remission assuming a relapse rate at 12 months of 30% in placebo group. The primary outcome measure was the rate of relapse analyzed by the X^2 test. Please note: The Chi Square statistic compares the tallies or counts of categorical responses (such as relapse, maintenance of remission) between two (or more)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			groups.								independent groups. Chi square tests can only be used on actual numbers and not on percentages, proportions, means, etc. Note: primary outcome measure is relapse, not maintenance of remission and that the treatment groups were analyzed by the X^2 test.

Effect Size			
Outcome Relapse at 1 year	Number of trials 1	Treatment vs. Control Budesonide 6 mg : 22/36 vs. 24/36 Budesonide 3mg : 23/33 vs. 24/36 Cochrane review shows maintenance of remission as the total population less number relapsed. Cochrane data agrees with above Ford et al combines doses. Totals agree with above	RR (95% CI) 0.92 (0.65 to 1.30) 1.05 (0.76 to 1.44)
Relapse at one year plus withdrawals – data not provided	1	No data	No data
Adverse events –cortisol levels (continuous) at	1	Baseline changes	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
one year				Budesonide 6 mg vs. placebo: 266 + 272 vs. 367 + 200 Budesonide 3 mg vs. placebo: 367 + 358 vs. 367 + 200			Mean difference -101.00 [-211.29 to 9.29] Mean difference 0.00 [-138.52 to 138.52] No significant difference between the groups and changes from baseline and mean values at 12 months (per author)				
IBDQ score			1	Budesonide 6 mg vs. placebo: 161 + 36 vs. 150 + 38 Budesonide 3 mg vs. placebo: 156 + 39 vs. 150 + 38			Mean difference 11.00 [-6.10 to 28.10] Mean difference 6.00 [-12.20 to 24.20] No significant difference between baseline and mean values at 12 months (per author)				

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 1807 Gross et al, 1998[33] Country: Germany	RCT	179 patients	Inclusion: ages 10-70 years in remission with 10 mg or 5 mg prednisolone equivalent for eight weeks Demographic characteristics: Patient characteristics were similar with regard to gender, age, duration of disease, previous therapy, location of disease, CDAI at randomisation	3 mg budesonide	Placebo	1 year	Relapse defined as an increase of the CDAI to at least 150 for more than two subsequent weeks or a CDAI of at least 150 at the end of the study or at the last documented visit. Secondary outcome measures were time to relapse and side effects.	See table below	Dr. Falk Pharma, Freiburg, Germany	Oral	The initial sample calculation required 100 patients in each group to show a reduction of the recurrence rate by one third (ITT population: 84 Budesonide and 95 placebo). The study was terminated prematurely as the overall failure rate was high.

Effect Size

Outcome	Number of trials	Treatment vs. control	RR (95% CI)
Relapse at 1 year	1	3 mg budesonide vs. placebo: 56/84 vs. 62/95 Study not included in Cochrane review.	1.02 (0.83 to 1.26)
Relapse + withdrawal Calculated by subtracting patients in remission (20 in budesonide arm and 19 in placebo arm) from total sample size	1	3 mg budesonide vs. placebo: 64/84 vs. 76/95	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Withdrawal due to adverse events			1	Budesonide 3 mg vs. placebo: 2/84 vs. 4/95			0.57 (0.11 to 3.01)				

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 236 Hanauer et al, 2005[34] Country: USA	RCT	110 patients at 22 centres in the USA	Inclusion: 18 years or older with CD of distal ileum and/or proximal colon. Patients were recruited from a preceding study in which 8 weeks of treatment with Budesonide 9 mg/day was compared with placebo. CDAI < 150. Demographic characteristics: The baseline characteristics of the two treatment groups were similar with regard to age, gender, weight, disease location, prior resection, previous treatment in induction trial and baseline CDAI.	6 mg budesonide daily	Placebo	1 year	Time until relapse as defined by CDAI > 150 together with an increase of at least 60 points from value at entry into the study or clinical deterioration of CD. Adrenal insufficiency Withdrawals	See table below	AstraZeneca	Oral	2 of the 110 patients (one in each arm) randomised were not in remission at time of randomisation but were included in the analysis 65 of 110 patients randomised did not complete the study

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Effect Size											
Outcome			Number of trials	Treatment vs. control							
Relapse at one year			1	Budesonide 6 mg vs. placebo: 26/55 vs. 32/55 Data agrees with Ford et al.			0.81 (0.57 to 1.16)				
Relapse + withdrawals at one year (Withdrawals due to adverse events, non-compliance with study medications or study procedures, loss to follow-up, non-allowed concomitant medication and miscellaneous other reasons)			1	Budesonide 6 mg vs. placebo: 30/55 vs. 35/55 Data not reconciled with Cochrane or Ford et al.			RR 0.86 (0.63 to 1.17)				
Withdrawal due to adverse events			1	Budesonide 6 mg vs. placebo: 10/55 vs. 10/55			1.00 (0.45 to 2.21)				

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 516 Lofberg et al, 1996[35] Country: 7 European countries, including UK	RCT	90	Inclusion: Aged 18 or more who had achieved remission (CDAI < 150) after 10 weeks' treatment with either budesonide or prednisolone Demographic characteristics: The treatment groups were similar with regard to age, disease location, induction drug. There were somewhat lower initial CDAI scores in the 6mg budesonide group and a larger proportion of women in the 3 mg group no significant differences). There was a skewed allocation regarding previous treatment with prednisolone: 6 mg budesonide 72%; 3 mg budesonide 35% and placebo 52%.	Budesonide 6mg Or budesonide 3 mg	Placebo	1 year	CDAI > 150 together with an increase of at least 60 points or patients who were withdrawn from the study and who required medical or surgical treatment. Time to relapse Withdrawals	See table below	Astra Draco	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Effect Size											
Outcome			Number of trials		Treatment vs. control		RR (95% CI)				
Relapse at one year (therapeutic failure)			1		Budesonide 6 mg vs. placebo 15/32 vs. 17/27 Budesonide 3 mg vs. placebo 21/31 vs. 17/27 Data not reconciled with Cochrane or Ford et al		0.74 (0.47 to 1.19) 1.08 (0.7 to, 1.57)				
Relapse (therapeutic failure) + withdrawal (adverse events [i.e. constipation and pregnancy in 2 placebo patients], withdrawal of informed consent and desire to become pregnant.)			1		Budesonide 6 mg vs. placebo 18/32 vs. 20/27 Budesonide 3 mg vs. placebo 22/31 vs. 20/27 Ford et al combines doses. Totals agree with above Data not reconciled with Cochrane		0.76 (0.52 to1.11) 0.96 (0.7 to, 1.32)				
Abnormal response to ACTH hormone (Basal plasma cortisol concentration was at least 150 nmol per litre and either the post stimulation value at 30 or 60 minutes increased by at least 200 nmol per litre or had increased to more than 400 nmol per litre)			1		Budesonide 6 mg vs. placebo 5/23 vs. 0/13 Budesonide 3 mg vs. placebo 2/21 vs. 0/13		6.42 (0.38 to 107.55) 3.13 (0.16 to 61.49)				
Withdrawal due to adverse events			1		Budesonide 6 mg vs. placebo 0/32 vs. 2/27 Budesonide 3 mg vs. placebo 0/31 vs. 2/27		0.17 (0.01 to 3.39) 0.17 (0.01 to 3.49)				

1.2.3.2 Economic evidence tables – budesonide for maintaining remission

Cost effectiveness of Entocort (oral budesonide) capsules as maintenance therapy for Crohn's disease in Sweden, Lofberg, R.; Hertzman, P., Research and Clinical Forums 1999, 20(3): 41-47				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA **Study design:** Markov decision analytic model **Approach to analysis:** To reflect the management of Crohn's disease in Sweden **Perspective:** Swedish healthcare service (healthcare payer) **Time horizon:** 1 year **Treatment effect duration:** 1 year **Discounting:** Costs: N/A; Outcomes: N/A	**Population:** Patients with Crohn's disease affecting the ileocaecal area, and who have had a recent exacerbation and have been brought into remission **Cohort settings:** Start age = NR Male/Female = NR **Intervention 1:** Entocort capsules (6 mg/day for 8 weeks as maintenance therapy) (Patients were brought into remission with 9mg/day Entocort or prednisolone) **Intervention 2:** Prednisolone (40mg/day starting dose, no maintenance therapy)	**Total costs (mean per patient):** Entocort: $3,490 (£2,277) No maintenance therapy): $3,290 (£2,147) Incremental (1-2): $200 (£131) (CI , ; p = NR) **Currency & cost year:** 1999 US dollars presented here as 1999 UK pounds‡ **Cost components incorporated:** Cost of relapse, cost of surgery (weighted by the probability of incurring the cost of treating complications due to surgery), cost of maintenance therapy	**Primary outcome measure:** Number of relapses (mean per patient) Entocort: 0.78 No maintenance therapy: 1.06 Incremental (1-2): -0.28 (CI ,p = NR) **Other outcome measures (mean):** Average days in remission Entocort: 288 No maintenance therapy: 271 (p = NR)	**Primary ICER (Entocort vs No maintenance therapy):** ICER: $12 (£8) per day in remission, equivalent to £2,920 per year in remission (d/a) CI: N/A Probability cost-effective: N/A **Subgroup analyses:** N/A **Analysis of uncertainty:** A number of one-way sensitivity analysis conducted involving (i) changing second-line acute success rate from 50% to 65% (ii) probability of surgery at relapse and after failure of first-therapy from 10% to 5% (iii) varying the costs of relapse, cost of surgery by +/- 25% and cost of second-line therapy +/- 25% of the base case. Changing the second-line acute therapy success rate from 50% to 65% did not have a significant impact on the economic results. Varying the cost of relapse had minor impacts on the cost-effectiveness results whilst varying the cost of surgery had the greatest impact.
Data sources				
Health outcomes: Clinical trials of oral budesonide (Campieri et al. 1997; Feagan et al. 1997; Greenberg et al. 1994, 1996; Lofberg et al. 1996; Rutgeerts et al. 1994; Thomsen et al. 1997), Swedish data sources (probabilities of a relapsing patient to have drug therapy or surgery, for example, where obtained from treatment profiles developed by three Swedish clinical experts). **Quality-of-life weights:** N/A **Cost sources:** Huddinge University Hospital, Swedish pharmaceutical prices, questionnaires and face-to-face interviews				
Comments				

Cost effectiveness of Entocort (oral budesonide) capsules as maintenance therapy for Crohn's disease in Sweden, Lofberg, R.; Hertzman, P., Research and Clinical Forums 1999, 20(3): 41-47
Source of funding: NR; **Limitations:** Modelling was undertaken over a short time horizon and no probabilistic sensitivity analysis was conducted.
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

*Abbreviations: CEA = cost-effectiveness analysis; CI = confidence interval; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis ‡ Converted using 1999 Purchasing Power Parities [http://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP] * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Cost effectiveness of budesonide controlled ileal release (CIR) capsules as maintenance therapy versus no maintenance therapy for ileocaecal Crohn's disease in Sweden, Noble, I.; Brown, R.; Danielsson, A.; Ericsson, K.; Floren, C.H.; Hertzman,P.; Lofberg, R., Clinical Drug Investigation, 1998 15(2): 123-136

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CEA **Study design:** Markov **d**ecision analytic model **Approach to analysis:** Compare budesonide maintenance therapy with no active maintenance therapy of Crohn's disease in Sweden **Perspective:** Swedish third-party payer perspective **Time horizon:** 1 year **Treatment effect duration:** 1 year **Discounting:** Costs: N/A ; Outcomes: N/A	**Population:** Patients with Crohn's disease affecting the distal ileum and the ascending colon who had had a recent exacerbation (within 10 to 12 weeks) and have been brought into remission **Cohort settings:** Start age = 36 years (for maintenance treatment group), 34 years (for no maintenance therapy group) Male/Female = NR **Intervention 1:** Budesonide CIR (Entocort) capsules (6 mg/day as maintenance therapy) **Intervention 2:** No active maintenance therapy (budesonide prescribed if patient has relapse and second-line acute therapy is total parenteral nutrition with methylprednisolone, or elemental diet)	**Total costs (mean per patient):** Entocort: SEK 27,945 (£1,924) No maintenance therapy: SEK 26,272 (£1,809) Incremental (1-2): SEK 1,673 (£115) (CI , ; p=NR) **Currency & cost year:** 1998 Swedish Kronor (SEK) presented as 1998 UK pounds‡ **Cost components incorporated:** Cost of relapse, cost of surgery, cost of maintenance therapy	**Primary outcome measure:** Number of days in remission Entocort: 288.1 No maintenance therapy: 271.5 Incremental (1-2): 16.6 (CI , ; p=NR) **Other outcome measures (mean):** Average number of relapses Entocort: 0.78 No maintenance therapy: 1.06 (p= NR)	**Primary ICER (Entocort vs No maintenance therapy):** ICER: SEK 101 (£7) per additional day in remission, equivalent to £2,555 per year in remission (d/a) CI: N/A Probability cost-effective: N/A **Other:** incremental cost per QALY of SEK 101,394 (£6981) [estimated using utility values derived by an expert panel of gastroenterologists] **Subgroup analyses:** N/A **Analysis of uncertainty:** A number of one-way sensitivity analysis conducted involving (i) changing second-line acute success rate from 50% to 65% (ii) probability of surgery at relapse and after failure of first-therapy from 10% to 5% and 15% (iii) varying the costs of relapse, cost of surgery by +/- 25% and cost of second-line therapy +/- 25% of the base case, and (iv) equal average number of hospitalizations. The model results were robust to changes in most of the parameters; cost items surgery and second-line acute therapy (requiring inpatient care) had the largest impact on cost-effectiveness. Using the Swedish average cost of surgery, which is higher than was the cost at Huddinge University Hospital, gives an ICER of SEK 26 (£2) per day in remission

Data sources

Health outcomes: Clinical trials of budesonide CIR capsules in maintenance treatment (Campieri et al. 1997; Feagan et al. 1997; Ferguson et al. 1998; Greenberg et al. 1994, 1996; Lofberg et al 1996; Rutgeerts et al 1994; Thomsen et al. 1997), clinical opinion

Cost effectiveness of budesonide controlled ileal release (CIR) capsules as maintenance therapy versus no maintenance therapy for ileocaecal Crohn's disease in Sweden, Noble, I.; Brown, R.; Danielsson, A.; Ericsson, K.; Floren, C.H.; Hertzman,P.; Lofberg, R., Clinical Drug Investigation, 1998 15(2): 123-136
Quality-of-life weights: HRQoL scores reported in study by Trallori and Messori 1997[36], and estimated by an expert panel of gastroenterologists **Cost sources:** Huddinge University Hospital, Swedish pharmaceutical prices, questionnaires and face-to-face interviews
Comments
Source of funding: Study part funded by industry; **Limitations:** Modelling was undertaken over a short time horizon and no probabilistic sensitivity analysis was conducted.
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

*Abbreviations: CEA = cost-effectiveness analysis; CI = confidence interval; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 1998 Purchasing Power Parities [http://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP] * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

1.2.3.3 Budesonide versus mesalazine for maintaining remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 179 Mantzaris et al, 2003[37] Country: Greece	RCT	57	Inclusion: Patients between 18-65 years with CDAI < 150 and glucocorticosteroid dependence. Glucocorticosteroid dependence defined as having received at least 2 courses of glucocorticosteroid in preceding 12 months, with a relapse of disease before stopping the glucocorticosteroid. Patients were maintained on lowest dose of prednisolone necessary to keep disease in remission. Demographic characteristics: No statistically significant	6mg Budesonide; at randomisation prednisolone was switched to Budesonide 6mg/day	Mesalazine 1 g 3 times/day; prednisolone was further tapered off (decreased by 5 mg/week) and stopped over the first 1-3 weeks of the study	1 year	Relapse (CDAI > 150 and > 100 from baseline); changes in health-related quality of life; changes in CDAI; time to relapse; time to discontinuation of prescribed drug.	See table below			Sample size calculations for 30% difference in relapse rates with 80% probability assuming an annual relapse rate of 50% for budesonide was 32 patients per group. Thus, the study was underpowered.

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			difference in clinical and demographic characteristics of treatment groups with regard to gender, age, weight, smoking, disease location, entry CDAI, time in remission, mean maintenance dose of glucocorticosteroid.								

Effect Size			
Outcome	Number of trials	Budesonide vs. mesalazine	RR (95% CI)
Relapse at one year – all withdrawals were the result of therapeutic failure	1	Budesonide 6 mg/day vs. mesalazine 3 g/day. 16/29 vs. 23/28 Data agrees with Cochrane review. Study not included in Ford et al	0.67 (0.46 to 0.97)
Mean time to relapse or discontinuation of treatment	1	Budesonide 6 mg/day vs. mesalazine 3 g/day. 241 + 114 days vs. 147 + 117 days	Mean difference: 94.00 [34.00 to 154.00] favours budesonide
IBDQ scores at one year	1	Budesonide 6 mg/day vs. mesalazine 3 g/day. 150 [SD, 58.07] vs. 113 [SD, 33] (95% CI 15.93-58.07)	Mean difference: 37.00 [16.85 to 57.15] favours budesonide P < 0.0001 (per authors)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Withdrawal due to adverse events			1		None in either group			NA GRADE table not done			

1.2.3.4 Budesonide versus prednisolone for maintaining remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 237 Schoon et al, 2005[38] Country: Multi-national including UK	Unblinded RCT	90 glucocortic osteroid-dependant patients with quiescent disease	Inclusion: Patients aged 20-70 years with either: 1 Mild to severe active CD CDAI > 150) and were glucocorticoster oid- free and had not received glucocorticoster oid during previous 6 months; 2. Glucocorticoster oid-dependent patients with quiescent disease (CDAI < 200) on prednisolone 7-20 mg/day for at least 4 of the preceding 6 months. Demographic characteristics: Across the strata the patients were similar in all	Budesonide 9 mg/day	Pre-existing prednisolone regime	24 months	Bone mineral density (not outcome of interest); Maintenance of remission Withdrawals due to AEs Withdrawals to CD deterioration or not improved	See table below	AstraZeneca, Sweden	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treat-ment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			baseline characteristics including gender, age, BMI, disease duration CDAI (133 in glucocorticosteroid-dependent patients) and smoking.								

Effect Size

Outcome	Number of trials	Treatment vs. control	RR (95% CI)
Relapse (withdrawal due to CD deterioration or not improved, i.e. therapeutic failure)	1	Budesonide 9 mg/day vs. prednisolone 40 mg/day 19/46 vs. 11/44 Agrees with Cochrane	RR 1.65 (0.89 to 3.06)
Relapse + withdrawal due to adverse events or 'other'	1	Budesonide 9 mg/day vs. prednisolone 40 mg/day 26/46 vs. 19/44 Data not reconciled to Cochrane	RR 1.31 (0.86 to 2.00)
Withdrawal due to Adverse Events	1	Budesonide 9 mg/day vs. prednisolone 40 mg/day 4/46 vs. 0/44 Agrees with Cochrane	RR 8.62 (0.48 to 155.52)
Adrenal suppression (abnormal ACTH Stimulation Test)	1	Budesonide 9 mg/day vs. prednisolone 40 mg/day 13/36 vs. 20/33 *numbers from Cochrane review – accessible in paper only as graph	RR 0.60 (0.36 to 1.00)

1.2.4 Azathioprine/mercaptopurine for maintaining remission

1.2.4.1 Azathioprine versus placebo for maintaining remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6335 O'Donoghue et al, 1978[39] Country: UK	DB RCT		51	Inclusion: Outpatients with CD in remission or stable good health while taking AZA (2 mg/kg/day) for ≥ 6 months. Patients receiving sulfasalazine or low doses of glucocorticosteroid in addition to AZA were included provided that such treatment remained unaltered throughout the study Randomisation occurred after stratification according to whether or not participants took concomitant anti-inflammatory	Group 1: Continued treatment with AZA (2 mg/kg/day)	Group 2: AZA replaced by placebo tablets	Until relapse or 12 months	Relapses (Defined as significant deterioration in clinical state requiring treatment change) Adverse events Withdrawal due to adverse events	See effect size table	Joint Research Board of St. Bartholomew's hospital. And St. Mark's Research Foundation	Oral

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				drugs. This ensured that the two groups (AZA vs. Placebo) were comparable for size and distribution. Demographic comparison: Treatment groups were similar for age (21–78 years), gender, pre-trial disease activity score and duration of disease. 17 (placebo) and 11 (AZA) patients had disease located in the colon. 10 (AZA) and 3 (placebo) had ileocolic disease. 7 (placebo) and 3 (AZA) had disease in the small bowel.						

Effect Size

There were 3 relapses among the 15 patients who were also taking prednisolone and/or sulfasalazine and 7 relapses among the 36 patients not taking these drugs. It was not specified which treatment group patients were allocated to.

Outcome	Number of	AZA vs. placebo	Result

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
					trials				RR (95% CI)		
Relapses[*] (at 12 months)					1	1/24 vs. 9/27			0.13 (0.02 to 0.92)		
Relapses plus withdrawals[†] (at 12 months)					1	4/24 vs. 11/27[‡]			0.41 (0.15 to 1.12)[‡]		
Adverse events					1	1[**]/24 vs. 0/27			3.36 (0.14 to 78.79)		
Withdrawal due to adverse events					1	1[**]/24 vs. 0/27			3.36 (0.14 to 78.79)		

[*] Defined as significant deterioration in clinical state requiring treatment change

[†] Five patients were withdrawn from the study (3 AZA, 2 placebo) for reasons other than a relapse (no further details were provided)

[‡] The Cochrane review[4] calculated maintenance of remission (13/23 vs. 8/27; OR 2.95 [0.97 to 9.00]). They defined remission as scores of 'unchanged or better' according to a disease activity scoring system (detailed in Willoughby et al. 1971[40]). This scoring system did not comply with the protocol for this review question.

[**] Death due to infection after pancytopenia developed

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6334 Lémann et al. 2005[41] Country: France (11 sites), Belgium (1 site)	DB RCT	83	Inclusion: Adults (≥ 18) in clinical remission on continuous AZA for ≥ 42 months. No flare-up; no treatment with oral prednisone (> 10 mg/day), budesonide, artificial nutrition, or other immunosuppressive or biological treatments; and no surgery (except limited perianal surgery) during preceding 42 months. No treatment with rectal glucocorticosteroid, aminosalicylates, metronidazole or ciprofloxacin during preceding 6 months. Patients were excluded if they had active disease (CDAI score > 150 at entry); Crohn's disease limited to perianal area or were treated with AZA for prevention of postoperative recurrence after	Group 1: Continue AZA (1.7 mg/kg/day ± 0.4 [mean ± SD])	Group 2: Placebo	18 months	Relapses (Defined as a CDAI score > 250, a CDAI score of 150 – 250 on 3 consecutive weeks with an increase of ≥ 75 points above the baseline value, or the need for surgery for Crohn's disease [except limited perianal surgery]) Adverse events Withdrawal due to adverse events	See effect size table	Grant supports from Société Nationale Française de Gastroentérologie and by the Association François Aupetit. Drugs were provided by GSK.	Oral

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				curative surgery Demographic comparison: Groups comparable for age (AZA: 40 ± 14; placebo: 36 ± 11), gender, number of smokers, disease site, duration of disease, remission and AZA treatment, AZA dose, CDAI score and perianal lesions							

Effect Size

Outcome	Number of trials	AZA vs placebo	Result RR (95% CI)
Relapses at 12 months[¶]:	1	2/40 vs. 7/43[§]	0.31 (0.07 to 1.39)[§]
Relapses plus withdrawals at 12 months[‡]:	1	6/40 vs. 8/43[§]	0.81 (0.31 to 2.12)[§]
Relapses at 18 months[¶]:	1	3/40 vs. 9/43	0.36 (0.1 to 1.23)
Relapses plus withdrawals at 18 months[†]:	1	17/40 vs. 16/43	1.14 (0.67 to 1.94)
Adverse events at 12 months	1	2[*]/40 vs. 1[¥]/43	2.15 (0.20 to 22.81)
Withdrawal due to adverse events at 12 months	1	1[**]/40 vs. 1[¥]/43	1.07 (0.07 – 16.62)

¶ Defined as a CDAI score > 250, a CDAI score of 150 – 250 on three consecutive weeks with an increase of ≥ 75 points above the baseline value, or the need for surgery for Crohn's disease (except limited perianal surgery)

‡ 5 patients (4 AZA, 1 placebo) were withdrawn from the study at 12 months for reasons other than a relapse (AZA: 2 withdrew consent, 1 adverse event, 1 not reported; placebo: 1 withdrew consent)

† 21 patients (14 AZA, 7 placebo) were withdrawn from the study at 18 months for reasons other than a relapse (AZA: 2 withdrew consent, 1 adverse event, 11 not reported; placebo: 2 withdrew consent, 1 adverse event, 4 not reported)

§The Cochrane review[4] calculated maintenance of remission instead of relapse, which they defined as patients not experiencing a relapse (38/40 vs. 36/43; OR 3.17 [0.80 to 12.54]).

**1 death (patient diagnosed with a myelodysplastic syndrome with bone-marrow karyotype abnormalities in chromosome 7 at 6 months; died 6 months later); 1 mild leukopenia (led to AZA dose reduction)*

¥ Facial rash

*** 1 death (patient diagnosed with bone-marrow karyotype abnormalities in chromosome 7 at 6 months, died 6 months later)*

¥ Facial rash
*** 1 death (patient diagnosed with bone-marrow karyotype abnormalities in chromosome 7 at 6 months, died 6 months later)*

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 5 Summers et al. 1979[13] Singleton et al. 1979[14] Winship et al. 1979[42] Country: USA	DB RCT		155	Inclusion: Patients with quiescent disease or complete resection of all actively diseased tissue within year of study entry (CDAI < 150). Patients were stratified based on whether they had received systemic glucocorticosteroid within 2 weeks of randomisation and whether disease was confined to the colon or not Demographic comparison: NSD for age (AZA: 31.6 ± 11.7; placebo: 31 ± 9.5) sex, race, duration of disease at randomisation, CDAI at randomisation, body weight, prior treatment with prednisone or sulfasalazine, prior abdominal surgery for Crohn's disease and location of the	Group 1: AZA (1 mg/kg/day)	Group 2: Placebo	2 years	Maintenance of remission (Defined as no flare-up. Flare-up defined as CDAI > 150 and over 100 points greater than initial CDAI for two consecutive weeks, need for operation, development of new fistula other than simple anal fistula, persistence of daily fever > 38.9 °C for > 14 consecutive days and interim barium X-rays worse than baseline X-rays) Adverse events Withdrawal due to adverse events	See effect size table	Not stated	Oral

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				disease in the bowel							

Effect Size

AZA was not associated with a significant prophylactic effect compared to placebo in patients who had received systemic glucocorticosteroid treatment within 2 weeks of randomisation or those who had not. However, the 89 patients who had received systemic steroid therapy within 2 weeks of randomisation had significantly better subsequent courses than the 185 patients who were not being treated with glucocorticosteroid at the time of randomisation ($p < 0.000001$). This analysis included patients allocated to treatments not discussed in this review (sulfasalazine [n = 58]; prednisone [n = 61]). 32 of 101 patients allocated to placebo and 17 of 54 patients allocated to azathioprine received prior glucocorticosteroid.

AZA was not associated with a significant prophylactic effect compared to placebo in patients with involvement only of the colon, only of the small bowel or both small and large bowel disease. However, the 248 patients with history or findings of involvement of the small bowel had a significantly more favourable course than the 26 patients with disease confined to the colon ($p < 0.000001$). This analysis included patients allocated to treatments not discussed in this review (sulfasalazine [n = 58]; prednisone [n = 61]). 9 of 101 patients allocated to placebo and 7 of 54 patients allocated to azathioprine had disease confined to the colon.

Outcome	Number of trials	AZA vs placebo	Result RR (95% CI)
Maintenance of remission at 12 months[*€]	1	37/54 vs. 65/101[ß]	1.06 (0.84 to 1.34)
Maintenance of remission at 24 months[*€]	1	10/54 vs. 23/101	0.81 (0.42 to 1.58)
Maintenance of remission at 24 months[*†]	1	10/35 vs. 23/57	0.71 (0.38 to 1.31)
Adverse events at 24 months: Disaster	1	2/54[¶] vs. 1/101[§]	3.74 (0.35 to 40.32)
Adverse events at 24 months: Severe	1	8/54[¥] vs. 7/101[‡]	2.14 (0.82 – 5.58)

** Defined as no flare-up. Flare-up defined as CDAI > 150 and over 100 points greater than initial CDAI for two consecutive weeks, need for operation, development of new fistula other than simple anal fistula, persistence of daily fever > 38.9 °C for > 14 consecutive days and interim barium X-rays worse than baseline X-rays*

€ Maintenance of remission analysed on an ITT basis (Follow-up data was available for all patients at 12 months)

ß These numbers agree with the Cochrane review [4]

† Maintenance of remission analysed according to censoring at 12 months; 92 patients entered the study at such a time that could be followed for 24 months

¶ 1 – leukopenia (hospitalised); 1 – fever (hospitalised)

§ 1 – thrombophlebitis (pulmonary embolus)

¥ 2 – pancreatitis; 1 – buttock abscess; 1 – diarrhoea following ostomy closure; 1 – herpes stomatitis; 1 – leukopenia; 1 – duodenal ulcer; 1 – recurrent peritonsillar abscess

‡ 2 – duodenal ulcer; 1 – arthritis and arthralgia; 1 – hypertension; 1 – nausea/vomiting; 1 – prostatitis; 1 – depression

1.2.5 Methotrexate for maintaining remission

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 254 Feagan et al., 2000[43] Country: Canada	RCT Multicentre		N = 76	Inclusion: Patients with chronically active Crohn's disease in remission following 25 mg once-weekly MTX IM injections for a minimum of 16 weeks Exclusion: Risk factors for MTX-induced toxicity including: hepatic disease, alcohol intake > 3 drinks/week, weight > 40% above normal, diabetes mellitus, renal dysfunction (serum creatinine > 1.7 mg/dL, clinically important lung disease, systemic infection, pregnancy/desire to become pregnant, history of cancer, or hypersensitivity to MTX. Demographic comparison: NSD in recorded baseline characteristics including age, gender, CDAI.	n = 40 Methotrexate 15mg IM one weekly *folic acid not routinely given, but started if AEs thought to be due to MTX	n = 36 Placebo	40 weeks 1 patient MTX group lost to follow-up, 17/40 discontinued treatment in MTX group, 23/36 discontinued treatment in placebo group	Relapse: increase in CDAI > 100 points above baseline, or initiation of prednisolone, an antimetabolite, or the two in combination for the treatment of Crohn's Absence of need for prednisolone Adverse events	See effect size table	Medical Research Council of Canada, Crohn's and Colitis Foundation of America, David and Minnie Berk Foundation, Crohn's and Colitis Foundation of Canada	Intramuscular injection

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Effect Size											
Outcome			Number of patients			Treatment vs. control RR (95% CI)			Notes		
Maintenance of remission			26/40 methotrexate 14/36 Placebo			Fixed-effects RR: 1.67 (1.05 to 2.67)			SS: Favours MTX		
Withdrawal due to adverse events			1/40 methotrexate 0/36 Placebo			Fixed-effects RR: 2.71 (0.11 to 64.43)			NS 1 MTX patient withdrew due to nausea		
Severe adverse events			0/40 methotrexate 2/36 Placebo			Fixed effects RR: 0.18 (0.01 to 3.64)			NS Cervical dysplasia, viral respiratory tract infection		

Incidence of adverse events reported in Feagan study*

Adverse event	Methotrexate n = 40	Placebo n = 36
Nausea and vomiting	16	9
Symptoms of a cold	10	10
Abdominal pain	7	9
Headache	7	6
Joint pain or arthralgia	5	10
Fatigue	5	5
Influenza-like illness	2	2
Diarrhoea	1	7
Abdominal bloating or distension	1	1
Rash	2	4

Adverse event	Methotrexate n = 40	Placebo n = 36
Insomnia	1	0
Other	17	15

*Patients may have had more than one adverse event

Please note that evidence on treatments for post-surgical maintenance of remission in Crohn's disease was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

1.3 Maintaining remission after surgery

1.3.1 5-aminosalicylate for maintaining remission after surgery

1.3.1.1 5-aminosalicylate versus placebo for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6526 Brignola et al. 1995[44] Country: Italy	RCT	87	Inclusion: Patients with curative resection of Crohn's disease (i.e. removal of all macroscopic disease in ileal or ileocaecal region). Demographic characteristics: Respective characteristics of mesalazine vs. placebo groups were as follows: Male 44 vs. 43; mean age in years 39 + 17 vs. 34 + 10; Mean duration of disease in months 75 + 73 vs. 69 + 54; more than 1 previous operation 13 vs. 11; ileal disease	Mesalazine (Pentasa) 2 x 500 mg tablets 3 times daily (i.e. 3 g/day) (n = 44) #US studies refer to this drug as mesalazine	Placebo (n = 43)	12 months, initiated within one month after surgery	Colonoscopy: description of type and characteristics of lesions; overall endoscopic severity (5-point scale from 0-4); "severe" recurrence (score 3-4). Or barium enema if colonoscopy unable to reach lesions. Overall severe recurrences = endoscopic score 3-4 or radiological documentation of recurrence. Clinical relapse (worsening of symptoms by at least 100 Crohn's Disease Activity Index points and attaining score >	See table below	Not stated	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			24 vs. 24; ileum + caecum 20 vs. 19.				150).				

Effect Size			
Outcome	Number of trials	Treatment vs. control Mesalazine vs. control	RR (95% CI)
Clinical remission	1	31/44 (70%) vs. 29/43 (67%)	RR 1.04 [0.79 to 1.39]
Clinical relapse (all of these also had endoscopic or radiologic evidence of recurrence)	1	7/44 vs. 10/43	RR 0.68 (0.29 to 1.63)
Relapse + withdrawal Withdrawals included 1 patient who moved, 1 patient who violated the protocol and 8 patients who withdrew due to adverse side effects	1	13/44 vs. 14/43	RR 0.91 [0.48 to 1.70]
Withdrawal due to adverse events	1	5/44 vs. 3/43	RR 1.63 [0.41 to 6.40]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6527 Ewe et al, 1989[43] Country: Germany	RCT	232	Inclusion: Patients having resection for Crohn's disease (radical or non-radical resection as customary in each participating centre); resection judged as curative by surgeon; no inflamed intestine left. Demographic characteristics: Patients in both groups were comparable in regard to age, previous surgeries, and site of involvement. There were 48 males in the sulfasalazine groups vs. 65 in the placebo	Sulfasalazine 3 g daily	Placebo	3 years, initiated while patient was in hospital	Crohn's Disease Activity Index (CDAI > 150); laboratory data; gastrointestinal tract examined radiologically, colonoscopy encouraged but not obligatory. Treatment failure defined as recurrence of Crohn's disease proven by radiology, endoscopy or operation.	See table below	Supported by the Deutsche Forschungsgemeinschaft grant Ew 4/12, 14, 16/1-3		

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			group.								
Effect Size											
Outcome			Number of trials		Treatment vs. control Sulfasalazine vs. placebo		RR (95% CI)				
Relapse in first year			1		18/111 (16%) vs. 34/121(28%)		RR 0.58 (0.35 to 0.96)				
Relapse + withdrawal in first year Withdrawals due to non-cooperation, technical reasons and medical reasons			1		40/111 vs. 59/121		RR 0.74 [0.54, 1.01]				
Relapse in first two years			1		27/111 vs. 46/121		RR 0.64 [0.43 to 0.95]				
Relapse + withdrawal in first two years Withdrawals due to non-cooperation, technical reasons and medical reasons			1		61/111 vs. 80/121		RR 0.83 [0.67to 1.03]				
Relapse in first three years			1		42/111 vs. 58/121		RR 0.79 [0.58 to 1.07]				
Relapse + withdrawal in first three years Withdrawals due to non-cooperation, technical reasons and medical reasons			1		89/111 vs. 99/121		RR 0.98 [0.86to 1.11]				

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6333 Hanauer et al, 2004[46] Country: USA	RCT	131	Inclusion: 1st or subsequent ileocolic resection with primary anastomosis with disease confined to the ileum and adjacent colon. Demographic characteristics: There were no statistical differences in patient age, sex, disease duration, indications for surgical resection or preoperative disease activity among patient groups.	(Mesalazine (Pentasa) 3 g daily (n = 44)	Placebo (n = 40)	2 years, initiated before post surgical discharge	% patients with relapse: Clinical assessment (1 = remission; 2 = mild symptoms; 3 = moderate symptoms; 4 = severe symptoms; clinical relapse = ≥ 2 on clinical recurrence grading scale);]; colonoscopy (Rutgeerts severity grading scale; (relapse ≥ 2); radiography (small bowel barium studies): 1 = normal; 2 = mucosal oedema/aphthoid ulcers; 3 = linear ulcers/ cobblestoning; 4 = strictures/ fistulas/ inflammatory mass; radiographic relapse ≥ 2	See table below	Crohn's and Colitis Foundation of America; David and Reva Logan GI Research Center, University of Chicago	Oral	

Effect Size

Outcome	Number of trials	Treatment vs. control	RR (95% CI)
		Mesalazine (Pentasa)[n = 44) vs. placebo [n = 40]	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Clinical recurrence rate at 24 months		1			58% (95% CI 41% to 75%) vs. 77% (95% CI 61% to 91%) 26/44 vs. 31/40		Hazard ratio 0.62; p = 0.123 RR 0.76 [0.57 to 1.03]				
Endoscopic recurrence at 24 months		1			63% (95% CI 47% to 79%) vs. 64% (95% CI 46% to 81%) 28/44 vs. 26/40		Hazard ratio 0.80, p = 0.458 RR 0.98 [0.71 to 1.35]				
Radiographic recurrence at 24 months		1			46% (95% CI 29% to 66%) vs. 49% (95% CI 30% to 72%) 20/44 vs. 20/40		Hazard ratio 0.61, p = 0.19 RR 0.91 [0.58 to 1.42]				
Total relapse + withdrawal Withdrawals due to surgical complication, adverse experience, noncompliance, lost to follow-up, pregnancy and withdrew consent.		1			33/44 vs. 35/40		RR 0.86 [0.70 to 1.05]				
Withdrawal due to adverse events		1			6/44 vs. 4/40		RR 1.36 [0.41to 4.48]				

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6521 Lochs et al, 2000[47] Country: Multicentre trial: Austria, Germany, Denmark, Norway	RCT	318	Inclusion: Patients 18-70 years of age who had respective surgery (radical (i.e. no lesions left, or non-radical) for a Crohn's disease-specific lesion; Crohn's diagnosed at least 6 months before surgery; complete investigation of digestive tract within 1 year before surgery; oral nutrition within 10 days of operation. Demographic characteristics: There were no significant differences between groups with regard to age, sex, duration of disease, location of disease, type of surgery, chronic activity,	(Mesalazine (Pentasa) 4g daily (divided into 3 doses of 1.5 g, 1 g and 1.5 g) n = 152	Placebo n = 166	18 months, initiated within 10 days after surgery	Clinical relapse defined by 1 of the following: increase in CDAI > 250; increase in CDAI above 200 but by a minimum of 60 points over lowest post-surgical value for 2 consecutive weeks; indication for surgery; development of new fistula; septic complication. Secondary: endoscopic relapse (Rutgeerts)	See table below	Ferring AS Denmark and Ferring Arzneimittel Germany	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			time since last acute phase and indication for surgery.								

Effect Size			
Outcome	Number of trials	Treatment vs. control Mesalazine vs. placebo	RR (95% CI)
Clinical relapse (CDAI > 250 or CDAI > 200 for two weeks) at 18 months	1	36/152 vs. 50/166	RR 0.79 [0.54 to 1.14]
Clinical relapse + withdrawal(loss to follow-up)	1	45/152 vs. 55/166	RR 0.89 [0.64 to 1.24]
Maintenance of remission	1	107/152 vs. 111/166	RR 1.05 [0.91 to 1.22]
Endoscopic recurrence at 18 months (colonoscopy done on 133 patients total)	1	40/61 vs. 36/72	RR 1.31 [0.98 to 1.76]
Serious adverse events	1	8/152 vs. 9/166	RR 0.97 [0.38 to 2.45]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6412 (McLeod et al, 1995[48]) Country: Multicentre, USA & Canada	RCT	163	Inclusion: Surgical resection for Crohn's disease; no gross residual disease; randomised within 8 weeks of surgery. Demographic characteristics: There were no significant differences between groups with regard to age, number of resections, site of disease.	Mesalazine 3 g/day (Rowasa l or Salofalk) n = 87	Placebo n = 76	A maximum of 72 months; patients randomised within 8 weeks of surgery	Symptomatic recurrent disease (symptoms severe enough to warrant treatment and radiological or endoscopic evidence of disease). Total recurrence (endoscopic or radiological evidence of disease (including both symptomatic, or asymptomatic patients)).	See table below	Ontario Ministry of Health, Interfalk Canada, Mount Sinai Hospital, Mayo Research Foundation	Oral	

Effect Size			
Outcome	Number of trials	Treatment vs. control Mesalazine vs. placebo	RR (95% CI)
Symptomatic recurrence rate (symptoms plus endoscopic and/or radiological confirmation of disease)	1	27/87 vs. 31/76	RR 0.76 [0.50 to 1.15]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6421 Wenckert et al, 1977[49] Country: Inter-Nordic Cooperative Study	RCT; double blind multicentre trial with block-randomisation and no cross-over.	66	Inclusion: Patients who were resected within one month of initiation of maintenance drug. Demographic characteristics: 33 women and 33 men with an age distribution from 15-59 years and a median age of 24 ½ years. The localisation at the time of operation was: jejunum 1, ileum 8, colon 15 and ileum + colon 42.	Salazosulfapyridine (Salazopyrin) 3 g/day	Placebo	18 months; treatment initiated within one month post-surgical.	Relapse was defined clinically, based on information from special control charts on the presence/absence of fever, diarrhoea, rectal haemorrhage, abdominal pain, extra-intestinal manifestations, palpable abdominal masses, fistulae, abscesses and possible loss of working days.	See table below	Not stated	Oral	

Effect Size

Outcome	Number of trials	Treatment vs. control Salazosulfapyridine vs. placebo	RR (95% CI)
Relapse at 12-15 months	1	4/32 (11.8%) vs. 7/34 (21.9%)	RR 0.61 [0.20 to 1.88]
Relapse at 12-15 months + withdrawal	1	20/32 (62.5 %) vs. 22/34 (70.6%)	RR 0.97 [0.67 to 1.39]
Relapse at 15-18 months	1	4/32 (11.8%) vs. 9/34(26.5%)	RR 0.47 [0.16 to 1.38]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Relapse at 15-18 months + withdrawal All withdrawn at end of study			1				NA				

1.3.2 Mercaptopurine for maintaining remission after surgery

1.3.2.1 Mercaptopurine versus placebo for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6333 Hanauer et al, 2004[46] Country: USA	RCT	131	Inclusion: First or subsequent ileocolic resection with primary anastomosis with disease confined to the ileum and adjacent colon. Demographic characteristics: There were no statistical differences in patient age, sex, disease duration, indications for surgical resection or preoperative disease activity among patient groups.	Mercaptopurine (50 mg) (n = 47)	Placebo (n = 40)	2 years, initiated before post-surgical discharge	% patients with relapse: Clinical assessment (1 = remission; 2 = mild symptoms; 3 = moderate symptoms; 4 = severe symptoms; clinical relapse = ≥ 2 on clinical recurrence grading scale);); colonoscopy (Rutgeerts severity grading scale; relapse ≥ 2); radiography (small bowel barium studies): 1 = normal; 2 = mucosal oedema/ aphthoid ulcers; 3 = linear ulcers/ cobblestoning; 4 =strictures/ fistulas/ inflammatory mass;	See table below	Crohn's and Colitis Foundation of America; David and Reva Logan GI Research Center, University of Chicago	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
							radiographic relapse ≥ 2				

Effect Size			
Outcome	Number of trials	Treatment vs. control mercaptopurine [n = 47] vs. placebo [n = 40]	RR (95% CI)
Clinical recurrence rate at 24 months	1	50% (95% CI 34% to 68%) vs. 77% (95% CI 61% to 91%) 24/47 vs. 31/40	Hazard ratio 0.52; p = 0.045 RR 0.66 [0.48 to 0.91]
Endoscopic recurrence at 24 months	1	43% (95% CI 28% to 63%) vs. 64% (95% CI 46% to 81%) 20/47 vs. 26/40	Hazard ratio 0.48, p=0.030 RR 0.65 [0.44 to 0.98]
Radiographic recurrence at 24 months	1	33% (95% CI 19% to 54%) vs. 49% (95% CI 30% to 72%) 16/47 vs. 20/40	Hazard ratio 0.57, p = 0.15 RR 0.68 [0.41to 1.13]
Total relapse + withdrawal Withdrawals due to surgical complication, adverse experience, noncompliance, lost to follow-up, pregnancy and withdrew consent.	1	32/47 vs. 35/40	RR 0.78 [0.62 to 0.98]
Withdrawal due to adverse events	1	9/47 vs. 4/40	RR 1.91 [0.64 to 5.75]

1.3.3 Azathioprine for maintaining remission after surgery

1.3.3.1 Azathioprine versus 5-ASA for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 1128 Ardizzone et al, 2004[50] Country: Italy	Open label RCT	140	Inclusion: Adult patients who underwent 'conservative' surgery (strictureplasty) for Crohn's disease Demographic characteristics: There were no significant differences between groups in age, sex, duration of disease, location of disease, fistula and abscess t surgery, surgical procedure, previous operations and CD therapy during the previous 6 months.	Mesalazine: 3 g/day in three divided doses n =71	AZA 2 mg/kg/day n = 69	24 months; initiated within two weeks of surgery	Clinical and surgical relapse. Clinical relapse was defined as the presence of symptoms related to CD, variably associated with radiologic, endoscopic, and laboratory findings, with a CDAI > 200. Surgical relapse was defined as the presence of symptoms refractory to medical treatment or complications requiring another surgical procedure (e.g. occlusive disease, intra-abdominal abscesses, or	See table below	Not stated	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
							high-flow fistulas).				

Effect Size			
Outcome	Number of trials	Treatment vs. control 5-ASA (Pentasa) vs. azathioprine	RR (95% CI)
Clinical relapse at 24 months	1	20/71 vs. 12/69	RR 1.62 [0.86 to 3.05] HR 1.63 (0.79 to 3.35)
Relapse + withdrawal (lost to follow-up [8] and withdrawal due to adverse events [21]) at 24 months *Not clear if withdrawals were included in the clinical relapse numbers reported above	1	30/71 vs. 31/69	RR 0.94 [0.65 to 1.37]
Surgical relapse	1	7/71 vs. 4/69	RR 1.70 [0.52 to 5.55] HR 1.48 (0.43 to 5.08)
Withdrawal due to adverse events	1	6/71 vs. 15/69	RR 0.39 [0.16 to 0.94]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6333 Hanauer et al, 2004[46] Country: USA	RCT	131	Inclusion: Primary or subsequent ileocolic resection with primary anastomosis with disease confined to the ileum and adjacent colon. Demographic characteristics: There were no statistical differences in patient age, sex, disease duration, indications for surgical resection or preoperative disease activity among patient groups.	Mesalazine (3 g)	Mercaptopurine (50 mg)	2 years; initiated before post-surgical discharge	% patients with relapse: Clinical assessment (1 = remission; 2 = mild symptoms; 3 = moderate symptoms; 4 = severe symptoms); clinical relapse = ≥ 2 on clinical recurrence grading scale); colonoscopy (Rutgeerts severity grading scale; relapse ≥ 2); radiography (small bowel barium studies): 1 = normal; 2 = mucosal oedema/ aphthoid ulcers; 3 = linear ulcers/ cobblestoning; 4 = strictures/ fistulas/ inflammatory mass; radiographic relapse ≥ 2	See table below	Crohn's and Colitis Foundation of America; David and Reva Logan GI Research Center, University of Chicago	Oral	
Effect Size											

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments

Outcome	Number of trials	Treatment vs. control (Mesalazine (Pentasa)[n = 44] vs. mercaptopurine [n = 47])	RR (95% CI)
Clinical recurrence at 24 months	1	58% (95% CI 41% to 75%) vs. 50% (95% CI 34% to 68%) 26/44 vs. 24/47	RR 1.16 [0.80 to 1.68]
Endoscopic recurrence at 24 months	1	63% (95% CI 47% to 79%) vs. 43% (95% CI 28% to 63%) 28/44 vs. 20/47	RR 1.50 [1.00 to 2.23]
Radiographic recurrence at 24 months	1	46% (95% CI 29% to 66%) vs.33% (95% CI 19% to 54%) 20/44 vs. 16/47	RR 1.34 [0.80 to 2.23]
Relapse + withdrawal (Withdrawals due to surgical complication, adverse experience, non-compliance, lost to follow-up, pregnancy and withdrew consent	1	33/44 vs.32/47	RR 1.10 [0.85 to 1.43]
Withdrawal due to adverse events	1	6/44 vs. 9/47	RR 0.71 [0.28 to 1.84]

1.3.4 Budesonide for maintaining remission after surgery

1.3.4.1 Budesonide versus placebo for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6522 Ewe et al, 1999[51] Country: Germany	RCT	83	Inclusion: Patients having curative resection for ileal, ileocolonic or colonic Crohn's disease and an anastomosis accessible to colonoscopy. Demographic characteristics: Characteristics of Budesonide (n = 43) vs. placebo (n = 40)groups respectively: Male 21 vs. 16; Female 22 vs. 24: age (years) 35 + 12 vs. 33 +9; duration of disease (months) 100 + 74 vs. 81 + 58; previous operations 25 vs. 27; ileal	Budesonide 1 mg capsule 3 times daily (n = 43)	Placebo (n = 40)	12 months; initiated while patients were still in surgical department	Recurrence of Crohn's disease based on colonoscopy at 3 and 12 months (modified Rutgeerts score) or rise in Crohn's Disease Activity Index [CDAI] from 60 up to 200 from the first follow up or CDAI > 200 and symptoms and signs of Crohn's disease where colonoscopy refused. Histology scores; CDAI; global judgement of well-being;	See table below	Budesonide supplied by Dr Falk Pharma, Freiburg	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			disease 12 vs. 9), colonic disease 5 vs. 7; ileal + colonic disease 26 vs. 24.)				time to recurrence. Clinical and blood status; symptoms and signs suggestive of side effects or recurrence				

Effect Size

Outcome	Number of trials	Treatment vs. control Budesonide (n = 43) vs. placebo (n = 40)	RR (95% CI)
Recurrence based on CDAI	1	8/43 vs. 11/40	RR 0.68 [0.30 to 1.51]
Recurrence based on endoscopic findings	1	16/30 vs. 19/27	RR 0.76 [0.50 to 1.15]
Withdrawal due to treatment failure	1	3/43 vs. 7/40	RR 0.53 [0.17to 1.68]
Withdrawal due to adverse events	1	1/43 vs. 1/40	RR 0.93 [0.06 to 14.38]
Withdrawal for any reason including treatment failure, non-compliance and side effects	1	14/43 vs. 17/40	RR 0.77 [0.44 to 1.34]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment		Effect size	Source of funding	Route of administration	Comments
Ref ID: 6523 Hellers et al, 1999[52] Country: Multicentre study in Sweden, France, England, Sweden, Germany, Italy, The Netherlands, Belgium	RCT	129	Inclusion: Patients having resection for ileocolonic Crohn's disease Demographic characteristics: Both groups were similar in terms of characteristics and disease history including sex, age, weight, previous resection time since resection reason for resection.	Budesonide controlled ileal release (CIR) 6 mg/day (Entocort) n = 63	Placebo n = 66	12 months; initiated within 2 weeks of surgery	Endoscopic scoring of mucosal inflammation (Rutgeerts); recurrence = score ≥ 2; Crohn's Disease Activity Index > 200; physician's global evaluation of patient's clinical status; laboratory values.	See table below	Astra Draco AB, Lund, Sweden	Oral	

Effect Size			
Outcome	Number of trials	Treatment vs. control Budesonide vs. placebo	RR (95% CI)
Recurrence based on endoscopic findings at new distal ileum at 12 months	1	33/63 vs. 38/66	RR 0.91 [0.66 to 1.24]
Recurrence based on endoscopic findings at anastomosis at 12 months	1	28/63 vs. 32/66	RR 0.92 [0.63 to 1.33]
Recurrence based on CDAI > 200 at 12 months	1	20/63 vs. 20/66	RR 1.05 [0.63 to 1.75]
Withdrawal due to adverse events	1	5/63 vs. 5/66	RR 1.05 [0.32 to 3.45]
Withdrawal due to any reason including treatment failure, adverse event, lost to follow up and other reasons.	1	23/63 vs. 18/66	RR 1.34 [0.80 to 2.23]

1.3.5 Metronidazole for maintaining remission after surgery

1.3.5.1 Metronidazole versus placebo for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6525 Rutgeerts et al, 1995[53]	RCT	57	Inclusion: Patients with Crohn's disease who underwent a curative resection of the distal ileum and partial colectomy with ileocolonic resection for complications of ileal Crohn's disease Demographics: Groups were similar with regard to age of onset, nature of disease, extent of disease.	Metronidazole (20 mg/kg) daily for three months Therapy was started as soon as possible after surgery, immediately after refeeding and always within 1 week after resection.)	Placebo	Patients were treated for 3 months and followed up at 6 month intervals up to 3 years by gastroenterologists not aware of the drug regimen received.	Primary endpoint was the presence and severity of endoscopic and histological recurrent lesions in the neo-distal ileum at 3 months and at three years. The second end point was clinical recurrence at 1, 2, and 3 years after surgery. Clinical recurrence defined as the appearance of symptoms	See table below	Roche, Belgium	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration	Comments
							interpreted by the treating physician as active disease.				

Effect Size			
Outcome	Number of trials	Treatment vs. control (Metronidazole vs. placebo	RR (95% CI)
Clinical recurrence at one year	1	2/29 vs. 7/28	0.28 (0.06 to 1.22)
Clinical recurrence at one year + withdrawal due to GI intolerance, acute paranoia, polyneuropathy, lack of compliance (6 metronidazole patients)	1	8/29 vs. 7/28	1.10 (0.46 to 2.64)
Clinical recurrence at two years	1	7/29 vs. 12/28	0.56 (0.26 to 1.22)
Clinical recurrence at two years + withdrawal due to GI intolerance, acute paranoia, polyneuropathy, lack of compliance (6 metronidazole patients)	1	13/29 vs. 12/28	1.05 (0.58 to 1.88)
Clinical recurrence at three years		9/29 vs. 14/28	0.62 (0.32 to 1.20)
Clinical recurrence at three years + withdrawal due to GI intolerance, acute paranoia, polyneuropathy, lack of compliance (6 metronidazole patients)		15/29 vs. 14/28	1.03 (0.62 to 1.72)
Endoscopic recurrence at three months	1	12/23 vs. 21/28	0.70 (0.45 to 1.09)
Endoscopic recurrence at three years		18/23 vs. 23/28	0.95 (0.72 to 1.26)
Withdrawal due to adverse events	1	5/29 vs. 0/28	10.63 (0.62 to 183.77)

1.3.6 Enteral nutrition for maintaining remission after surgery

1.3.6.1 Enteral nutrition versus placebo for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 687 Yamamoto et al, 2007[54] Country: Japan	Prospective cohort study	40 patients total: 20 high compliance patients (willing to insert NG tube and continue treatment for one year) And 20 low compliance patients	Inclusion: 40 consecutive patients who required resection of ileal or ileocolonic Crohn's disease. Demographic characteristics of total sample: Gender 154 females/26 males Mean age 32 years Duration of disease from diagnosis to surgery was 38 months. Four patients were smokers at the time of surgery. Eight patients had had previous ileocaecal resection for CD. All but three patients were treated with	EN (Elental) infusion by nocturnal NG tube All patients in both groups received mesalazine (Pentasa 3000 mg/day) during the entire study. No patients received glucocorticosteroid treatment, immune-suppressive drugs or infliximab before recurrent symptoms occurred.	Non EN diet	1 year	Recurrence as measured by CDAI > 150	See table below	Not stated	NG	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			glucocorticosteroid treatment for more than one month immediately before surgery. Thirty-one patients were also receiving mesalazine. Disease type: 26 penetrating/14 stricturing								

Effect Size			
Outcome	Number of trials	Treatment vs. control EN vs. Non-EN	Results RR (95% CI)
Clinical recurrence at one year (no withdrawals)	1	1/20 vs. 7/20	RR 0.14 [0.02 to 1.06]
Endoscopic recurrence at one year	1	6/20 vs. 14/20	RR 0.43 [0.21 to 0.89]

1.3.7 Metronidazole and azathioprine for maintaining remission after surgery

1.3.7.1 Metronidazole + azathioprine versus placebo + azathioprine for maintaining remission after surgery

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 6375 D'Haens et al, 2008[58] Country: Belgium	RCT	81	Inclusion: Patients aged 18-70 years having curative ileal or ileocolonic resection with ileocolonic anastomosis for Crohn's disease; 1 one more risk factors for the development of early/severe post-surgical recurrence (age < 30 years; active smoking; glucocorticosteroid use in the 3 months before surgery; 2nd, 3rd or 4th resection; perforating disease i.e. abscess or fistula as indication for surgery); women had to	Metronidazole 250 mg 3 times daily (or ornidazole 500 mg twice daily if metronidazole not tolerated) for three months + azathioprine (2 tablets [100 mg] if weight < 60 kg or 3 tablets [150 mg] if weight > 60 kg) for 12 months.	(Metronidazole 250 mg 3 times daily (or ornidazole 500 mg twice daily if metronidazole not tolerated) for three months + placebo for 12 months.	52 weeks; randomisation occurred within two weeks after surgery; initiated within two weeks of surgery	Proportion of patients with significant endoscopic recurrence (≥ 2 on Rutgeerts score for recurrence). Severity of endoscopic recurrence; Clinical relapse (CDAI > 250), adverse events	See table below	Partly Glaxo Smith Kline Wellcome	Oral	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of treatment	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			have negative pregnancy test and use adequate birth control. Demographic characteristics: There were no significant differences between groups with regard to age, sex, surgical history, smoking, AZA use in the past, steroid use at surgery and perforating disease.								

Effect Size			
Outcome	Number of trials	Treatment vs. control	RR (95% CI)
Clinical recurrences at 12 months (CDAI > 250)	1	3/40 vs. 7/41	RR 0.44 [0.12 to 1.58]
Clinical recurrences at 12 months (CDAI > 250) + withdrawal	1	11/40 vs. 19/41	RR 0.59 [0.33 to 1.08]
Endoscopic relapse (score ≥ 2) at 12 months	1	14/40 vs. 20/41	RR 0.72 [0.42 to 1.21]
Endoscopic relapse (score ≥ 2) + withdrawal at 12 months	1	22/40 vs. 32/41	RR 0.70 [0.51 to 0.97]
Withdrawal due to adverse events	1	2/40 vs. 2/41	RR 1.02 [0.15 to 6.93]

1.3.7.2 Economic evidence table - metronidazole and azathioprine for maintaining remission after surgery

Ananthakrishnan AN, Hur C, Juillerat P, Korzenik JR Strategies for the prevention of postoperative recurrence in Crohn's disease: results of a decision analysis Am J Gastroenterol. 2011 Nov;106(11):2009-17

Study details	Population & interventions****	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analysis **Approach to analysis:** A decision tree was constructed whereby the QALY gain was driven by the proportion of patients remaining in remission. In relapse, patients are given biologic induction therapy and if remission cannot be induced they undergo a second surgical intervention. **Perspective:** US- third party payer perspective **Time horizon:** one year	**Population:** Patients in surgically-induced remission of Crohn's disease following ileocecal resection. **Cohort settings:** Start age = 35 **Intervention 1:** No treatment **Intervention 2:** Azathioprine **Intervention 3:** Metronidazole	**Total costs (mean per patient):** **No treatment:** £2,587 **Metronidazole:** £1,872 **Azathioprine:** £2,121 **Currency & cost year:** Converted from 2011 USD to UK pounds using inflation factor of 0.66 taken from 2011 Purchasing power parity. **Cost components incorporated:** Drugs, surgery, colonoscopies, clinical recurrence (severe and moderate).	**Primary outcome measure:** QALYs (mean per patient) **No treatment:** 0.805 **Metronidazole:** 0.821 **Azathioprine:** 0.814	**ICER (azathioprine vs no treatment):** Azathioprine dominant. **ICER (azathioprine vs metronidazole):** Metronidazole dominant **Subgroup analyses:** Note that in the base case: R = 24%. **Low risk** (R = 10%): **ICER (azathioprine vs no treatment):** £24,245($36,750) **ICER (metronidazole vs no treatment):** £34,870 ($52,899) **High risk** (R = 49%): **ICER (azathioprine vs no treatment):** Azathioprine dominant. **ICER (azathioprine vs metronidazole):** Metronidazole dominant **Very high risk** (R = 78%): **ICER (azathioprine vs no treatment):** Azathioprine dominant. **ICER (azathioprine vs metronidazole):** Metronidazole dominant **One way sensitivity analysis:** ***

Data sources

Health outcomes: Efficacy for azathioprine and metronidazole were taken from a Cochrane review[56] which conducted meta-analyses using studies included in the clinical review[46,53,55,57].

Quality-of-life weights: Utility weights were taken from another economic analysis[58]; active disease, remission and surgery were assigned utility weights of 0.55, 0.83 and 0.40 respectively.

Ananthakrishnan AN, Hur C, Juillerat P, Korzenik JR Strategies for the prevention of postoperative recurrence in Crohn's disease: results of a decision analysis Am J Gastroenterol. 2011 Nov;106(11):2009-17
Original economic analysis for this guideline utilised utility weights of 0.61 and 0.89 for active disease and remission respectively which are the same in terms of their absolute difference (0.28). **Cost sources:** Costs came from US sources and therefore could not be verified. Key costs were compared to the UK equivalents as used in original economic analysis for this guideline and in general the costs used in this analysis were higher. The biggest discrepancy was in the cost of surgery; our model assumed the cost of surgery to be approximately £5,000 while this analysis used a value of around £8,000. This could have the effect of over-estimating the cost effectiveness of maintenance treatment, as relapses in the model become more costly.
Comments
Source of funding: The paper quotes that: 'Dr Korzenik has been a consultant for Procter & Gamble, Shire Pharmaceuticals and Cytokine Pharma, and receives research support from Procter and Gamble and Warner Chilcott…'., **Limitations:** Analysis conducted from US perspective; use of higher costs may have over-estimated the cost effectiveness of maintenance treatment. No formal probabilistic sensitivity analysis conducted.
Overall applicability*: Partially applicable **Overall quality**: Minor limitations**

Abbreviations: CI = confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; R = yearly baseline risk of relapse

* Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious Limitations/Very serious limitations

*** The model was run with alternative utility weights (remission = 0.86, active disease = 0.77, severe disease = 0.62). Azathioprine and metronidazole were still dominant versus no treatment with these utility values. The authors also state that azathioprine and metronidazole were still dominant at 'varying utilities for severe disease'. The model time horizon was extended from one to three years; metronidazole was still the preferred strategy and was dominant versus azathioprine and no treatment. No formal probabilistic sensitivity analysis was conducted. Mesalazine was used as the maintenance treatment of choice in a sensitivity analysis of 'treatment algorithm'. It was associated with an ICER of $3.2m per QALY gained. Uncertainty in treatment effects was explored by running the model with the upper and lower limits of their confidence intervals. When the model was run using the lower end of the confidence intervals for treatment effects, metronidazole remained the most cost-effective treatment. The authors stated: 'at the higher estimates of azathioprine effectiveness (RR = 0.38), this strategy would be more cost effective than metronidazole' . It is not clear from this statement whether azathioprine is cost-effective compared to metronidazole when the model is run with the upper limits of all the confidence intervals for all treatment effects, or just for azathioprine.

**** The model also included two biologic strategies- 'Tailored infliximab' and 'Upfront infliximab'. Neither strategy was cost-effective at a willingness to pay of £20,000 per QALY gained with the exception of 'Tailored infliximab' which was cost-effective (dominant) in the very high risk subgroup only

1.4 Enteral nutrition

1.4.1 Induction

1.4.1.1 Enteral nutrition versus conventional glucocorticosteroid for inducing remission in adults – Cochrane review

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
ID: 680 Zachos, et al[59] Enteral Nutritional Therapy for Inducing Remission of Crohn's Disease. Cochrane Database of Systematic Reviews, 2007.	SR: Moderate quality 6 studies included	Total n = 352 Range: 2-55	Inclusion: Patients with active Crohn's disease defined by a clinical disease activity index Studies: 1 paediatric, 5 adult	Enteral nutrition	Conventional Glucocorticosteroid	4 - 12 weeks	1. Induction of remission; CDAI < 150	See effect size table and GRADE table	Not stated

Outcome	Number of trials	Treatment vs. Control	Heterogeneity
1° outcome: induction of remission			
Enteral nutrition versus conventional glucocorticosteroid treatment	6	0.68 (0.57 to 0.80) Favours glucocorticosteroid	I^2 = 63%

1.4.1.2 Enteral nutrition versus conventional glucocorticosteroid for inducing remission in children – included in Cochrane review

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6425 Borrelli, 2006[60] Italy	RCT – open label		n = 37 (n = 41 but 4 children were excluded)	Inclusion: Children < 18yrs with Crohn's confirmed by recognized clinical, radiologic, endoscopic and histologic criteria Diagnosis within 12 weeks of enrolment Disease activity score in the mod-severe range Ability to start oral nutrition and oral medication Treatment with sulfasalazine or mesalazine if on a stable dosage for > 4 wks before study start date and were stopped ≥ 5 days before randomisation Exclusion: Fistulizing and/or anorectal Crohn's disease Stenosing Crohn's disease Pre-existing systemic disease Hepatic or renal dysfunction	N=19 Oral polymeric diet (Modulen) for 10 weeks. NGT if unable to introduce prescribed volume orally. Volume matched to 120-130% recommended Daily req. Clear oral fluids also permitted.	N=18 Oral glucocorticosteroid (methylprednisolone) 1.6 mg/kg/day (max. 60 mg/day) for 4 weeks, followed by 6 weeks of tapering down until 5-10 mg/day was reached.	10 weeks	Primary outcome Disease remission: PCDAI < 10 Endoscopic healing (CDEIS-Crohn's Disease Endoscopic Index of Severity) decrease in score of ≥ 50%. Histological healing (at least 3 samples taken) Healing of intestinal inflammation (when ≥ 50% reduction in endoscopic and histology scores) Secondary	See effect size table	Not reported	Oral or NGT to meet volume requirements for polymeric diet. Oral for glucocorticosteroid

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				Lung disease Systemic infection Suspected pregnancy Contraindication to glucocorticosteroid therapy Received glucocorticosteroid during the 4 wks prior to randomisation Previous treatment with azathioprine/ mercaptopurine, cyclosporine or other immunosuppressive agents at any time before enrolment Demographic comparison: Children Similar demographic characteristics Age range: Polymeric 4 – 16 yrs, glucocorticosteroid 4-17 yrs. Mean 11yrs and 12 yrs respectively. No statistical test results comparing the two groups are given.				outcomes Mean changes of the primary outcomes Adverse drug reactions Premature terminatio n of the study Weight BMI			

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Primary outcomes			1								
Induction of remission Disease remission: PCDAI < 10			1	Intention to treat: Polymeric 15/19 79% (95% CI 56 to 92%) Glucocorticosteroid 12/18 67% (95% CI 44 to 84%) p = 0.4 RR 1.18 (95% CI 0.79 to 1.77) Per-protocol analysis p = 0.6						
Endoscopic healing (CDEIS- Crohn's Disease Endoscopic Index of Severity) decrease in score of ≥ 50%.			1	Intention to treat: Polymeric: 15/19 79% (95% CI 56 to 92%) Glucocorticosteroid: 7/18 39% (95% CI 20 to 62%) p < 0.05 RR 2.03 (95% CI 1.09 to 3.79) Per-protocol analysis p < 0.05						
Histological healing (scoring system previously validated)			1	Intention to treat: Polymeric: 14/19 74% (95% CI 51-89%) Glucocorticosteroid: 6/18 (33%; 95% CI 16 to 57%) P < 0.05 RR 2.21 (95% CI 1.09 to 4.48) Per-protocol analysis p < 0.05						
Secondary Outcomes											
Mean changes of the primary outcomes			1	At 4 weeks, PCDAI was significantly lower in both groups compared to the baseline; polymeric 11.5 +/- 1.7, glucocorticosteroid 12.9+/- 3.01, p < 0.05. There was no significant difference in PCDAI score at baseline or at 4 weeks between the two groups.						
Adverse drug reactions			1	Total side effects: Polymeric 4/17 (23%, 95% CI 9 to 48%), glucocorticosteroid 11/15 (67%, 95% CI 41 to 85%), p < 0.05 RR 0.32 (95% CI 0.13 to 0.80) Abdominal pain: Polymeric 1/17 (6%), glucocorticosteroid 5/15 (33%) RR 0.18 (95% CI 0.02 to 1.35)						

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				Nausea +/- vomiting: Polymeric 3/17 (18%), glucocorticosteroid 4/15 (27%) RR 0.66 (95% CI 0.18 to 2.49) Flatulence: Polymeric 4/17 (23%), glucocorticosteroid 4/15 (27%) RR 0.88 (95% CI 0.27 to 2.93) Diarrhoea: Polymeric 2/17 (12%), glucocorticosteroid 0/17 RR 4.44 (95% CI 0.23 to 85.83) Cushingoid appearance: glucocorticosteroid 10/15 (67%) Acne: glucocorticosteroid 7/15 (47%) Skin striae: glucocorticosteroid 4/15 (27%) Hirsutism: glucocorticosteroid 3/15 (20%) Myopathy: glucocorticosteroid 2/15 (13%) Headache: glucocorticosteroid 2/15 (13%) Insomnia: polymeric 1/17 (6%), glucocorticosteroid 2/15 (13%) RR 0.44 (95% CI 0.04 to 4.39) Depression: glucocorticosteroid1/15 (7%)					
Premature termination of the study			1	Polymeric: 2/19 lost to follow up (inability to introduce the formula) Glucocorticosteroid: 3/18. 2 lost to follow up (worsening of disease activity) and 1 refused a repeat endoscopy RR 0.59 (95% CI 0.11 to 3.06)							
Weight			1	Weight gain: Polymeric 4.8kg +/- 0.5kg, glucocorticosteroid 3.2kg +/- 0.6 kg, $p < -0.05$							
BMI			1	Length gain – no significant difference between the two groups. Significant increase in BMI in each group. Polymeric BMI pre-trial 16.3+/-0.5 kg/cm^2, post trial 18.5+/-0.6 kg/cm^2, $p < 0.01$. Glucocorticosteroid BMI pre-trial 17.2+/-0.6 kg/cm^2, post-trial 19.3+/-0.8 kg/cm^2, $p < 0.01$							

1.4.1.3 Enteral nutrition versus conventional glucocorticosteroid in children for inducing remission – not in Cochrane review

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6427 Gorard, 1993[61] UK	RCT (stratified by malnourishment prior to randomisation)		n = 42 Adults	Inclusion: Active Crohn's disease requiring hospital admission with ≥ 1 of the following: abdominal pain causing severe limitation of activity diarrhoea (≥ 3 loose stools/day) weight loss of > 2 kg in the past month, or ≥ 2 laboratory abnormalities (Hb < 12.5 g/dl in men, Hb < 10.5 g/dl in women, ESR > 20 mm/h, serum albumin < 35 g/l) Exclusion: Evidence of intestinal obstruction Previous gastric surgery Contraindication to	n = 22 Elemental diet for 4 weeks (Vivonex TEN) No food. Coffee, tea and water allowed without milk.	n = 20 Prednisolone (0.75 mg/kg daily for 2 wks followed by reducing doses for 2 wks) No diet restriction.	1 year	Induction of remission[a]: DAI (Disease Activity Index) Remission at 6 months and 1 year Premature termination of the study Adverse events	See effect size table	Not reported	Elemental: Oral and NGT (if unable to take min. daily req. orally)

[a]Relapse: Clinical deterioration with an increase in DAI requiring high-dose glucocorticosteroid or return to a high dose for those having a tapering of the prednisolone, or surgery.

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				glucocorticosteroid Receiving > 7.5 mg prednisolone/day at time of relapse Demographic comparison: Age range 16-75 years. Mean (SD) 32.5yrs (3.4) prednisolone, 31.6 yrs (3.0) elemental. Well matched for age, site and duration of disease, nutritional state, initial DAI, laboratory and anthropometric data. No results given for chi-squared and Wilcoxon rank sum tests comparing the characteristics of the treatment groups.							

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity NA
Failure to achieve remission at 4 weeks	1	15% (3/20) of prednisolone-treated patients and 23% (3/13) of those tolerating elemental diet	

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
					RR 1.54 (0.36 to 6.49)						
Premature termination of study within 4 weeks – non-compliance			1		41% (9/22) of the elemental group withdrew due to lack of palatability and intolerance of NGT. Prednisolone withdrawals not reported.						
Premature termination of study – lack of efficacy/surgery rates			1		2/22 elemental patients (9%) and 1/20 on prednisolone (5%) deteriorated and required urgent colonic surgery RR 1.82 (0.18 to 18.55)						

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1958 O'Morain et al., 1984[62] UK	RCT Method of randomisation not given No mention of blinding No mention of allocation concealment		n = 21 17 adults; 4 children	Inclusion: Hospital patients with active Crohn's Adults and children Demographic comparison: Not comparable – Diet group 81% male, drug 50% male. No other baseline demographics given 4 paediatric cases in diet group, none in drug group (average age: 31.9 vs. 38.6)	Elemental diet (Vivonex) – free AA	Prednisolone 0.75 mg/kg	3 months	Improved Relapse Withdrawal Disease activity and remission criteria not defined	See effect size table	Norwich Eaton Laboratories, Wellcome Trust	Diet: Oral and NGT Drug: Not stated

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity NA
Improvement (measured at 4 weeks)		Diet 9/11 Drug 8/10 RR 1.02 (0.67 to 1.55) NS	

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6431 Ruuska, 1994[63] USA	RCT		n = 19 Children	Inclusion: Primary attack or relapse of Crohn's Diagnosis based on clinical, laboratory, endoscopic, histological and radiological findings Demographic comparison: Children aged 8.5 - 18.6 years. 7 boys, 12 girls	n = 10 Whole protein (casein) preparation for 8 weeks, then gradually reduced over 3 weeks and replaced by normal food. Water was permitted.	n = 9 Oral prednisolone (1.5 mg/kg/day up to a max 60 mg/wk) gradually reduced every week up to week 11	11 week trial with 0.3-2.5 years of f/u. Mean 1.3 years.	Induction of remission: PCDAI. No activity < 10, mild 11-30 and mod/high > 30. Adverse events Side effects Growth Premature termination of the study	See effect size table	Nutricia Pharmacia	Enteral nutrition given via an NGT for 12-14hrs during the day

Effect Size

Outcome	Number of trials	Treatment vs. control MD	Heterogeneity NA
Induction of remission: Change in PCDAI. No activity < 10, mild 11-30 and mod/high > 30.	1	At the outset: Enteral mean score (SD): 45 points (13.4) Glucocorticosteroid mean score (SD): 46 points (12.1) Mean difference: -1.00 (95% CI -12.47 to 10.47) At the end of 2 months, follow-up: Enteral mean score (SD): 11.9 points (7.9) Glucocorticosteroid mean score (SD): 14.3 points (9.6) Mean difference: -2.40 (95% CI -10.36 to 5.56) (not significant)	
Adverse events	1	Enteral: 1patient (1/10) underwent surgery for abdominal pain due to adhesions Glucocorticosteroid: 1 patient (1/9) underwent surgery	

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
					for obstruction RR 0.9 (95% CI 0.07 to 12.38)						
Side effects			1		Enteral – no side effects seen Glucocorticosteroid – typical accumulation of fatty tissue						

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1899 Zoli et al. 1997[64] Italy	RCT Method of randomisation not given No mention of blinding No mention of allocation concealment		n = 22	Inclusion: Adult clinic patients with active Crohn's Demographic comparison: Not formally tested, appear similar	Enteral Nutrition: Peptide-based elemental diet (Peptamen)	Drug treatment: Prednisolone 0.5 mg/kg/day	14 days	Remission – improvement Harvey Bradshaw Withdrawal	See effect size table	Associa-zione Ricerca in Medicina	Diet: Orally Drug: not stated

Effect Size

Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity NA
Induction of remission (improvement in HB over 2 weeks)		Diet: 8/12 Drug: 5/10 RR 1.33 [0.64 to 2.79] NS	
Withdrawal		Diet: 2/12 (intolerance)	

1.4.1.4 Enteral nutrition versus conventional glucocorticosteroid plus 5-aminosalicylate for inducing remission – children

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 899 Sanderson, 1987[65] Country: England	RCT		n = 17	Inclusion: Crohn's disease of the small bowel (barium follow-through, ileal histology of endoscopic biopsy) Clinical relapse of sufficient severity to warrant treatment with high dose glucocorticosteroid No treatment with glucocorticosteroid for the previous 12 months Incomplete skeletal maturation Domiciled in England (for follow-up) Demographic comparison: 12 boys and 5 girls Age 8.6 – 17.2 years No significant differences in the two groups: sex, age, disease	n = 8 Elemental nutrition (Flexical) for 6 weeks. Otherwise NBM. Then introduced to a normal diet for 6 weeks. Two children previously on sulfasalazine prior to the trial continued it.	High dose glucocorticosteroid: Adrenocorticotrophic hormone (2I U/kg/day) IM for five days followed by oral prednisolone (2 mg/kg/day to a max of 30 mg/day) and sulfasalazine (50 mg/kg/day). Glucocorticosteroid gradually reduced after 3 weeks aim for an alternate day regimen of 10 mg by 12 weeks.	12 weeks	Remission of disease: Lloyd-Still disease activity index score Growth Premature terminati on of the study	See effect size table	None reported Support from the Crohn's in Childhood Research Appeal	NGT for elemental nutrition

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
				activity, height SD score, ESR, CRP, Albumin or pubertal state.							

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	
Remission of disease: Lloyd-Still disease activity index score	1	At 6 weeks Elemental mean change in score (SE): 22 (2) Glucocorticosteroid mean change in score (SE): 17 (3) At 12 weeks Elemental mean change in score (SE): 22 (3) Glucocorticosteroid mean change in score (SE): 19 (4) MD 3.00 (-0.62 to 6.62)	
Growth		Mean height velocity for chronological age was significantly greater in the elemental group ($p < 0.05$) despite similar gain in weight	
Premature termination of the study	1	Two children were withdrawn. 1/9 elemental – was unwilling to forego normal diet. Patient was put on glucocorticosteroid. 1/8 glucocorticosteroid – developed clinical signs of bowel obstruction and underwent bowel restriction 2 weeks after commencing the glucocorticosteroid. RR 0.89 (0.07 to 12.00)	

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 1337 Terrin et al., 2002[66] Italy	RCT Method of randomisation not given Evaluating clinicians blinded No mention of allocation concealment		n = 20 Children	Inclusion: Children hospital patients with active Crohn's Demographic comparison: No baseline demographics	Enteral nutrition: Hydrolysed formula (Pregomin)	Drug treatment: methylprednisolone 1.6mg/kg/day + mesalazine 75 mg/kg/day	8 weeks	Remission : PCDAI < 10	See effect size table	Not stated	Diet: NGT Drug: Not stated

Effect Size			
Outcome	Number of trials	Treatment vs. control RR (95% CI)	Heterogeneity NA
Induction of remission by PCDAI	1	*Note: At end of 8 week trial both treatments had been effective in reducing PCDAI p < 0.01 Diet: 9/10 Drug: 5/10 RR 1.80 [0.94 to 3.46] NS between groups in response	
Withdrawal		0 in both groups - No side effects reported	

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 2239 Thomas et al, 1993[67] Country: UK	RCT		24 children with active Crohn's disease and 17 healthy controls	Inclusion: Children with active CD by Lloyd-Still activity index Demographic comparison: Glucocorticosteroid group 0.7 (mean) years younger and were also shorter and lighter weight than mean height and weight in elemental diet group. 7 children in the glucocorticosteroid group were considered to be 'wasted' (< 90% expected weight) and 4 children in enteral nutrition group were categorised as 'wasted.'	Normal diet; sulfasalazine 25 mg/kg/day and prednisolone 2 mg/kg/day with reduction of prednisone after two weeks if improvement noted	Enteral nutrition for four weeks; then normal foods were gradually introduced.	6 months	Disease activity (measured by Lloyd-Still activity index); Duration of remission; Height velocity	See effect size table	Northwestern Regional Health Authority	Oral for all but one patient who required NG tube

Effect Size			
Outcome	Number of trials	Treatment vs. control	Heterogeneity

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Change in disease activity			1		Change in disease activity by Lloyd-Still index from week 0 - week 4: All patients on glucocorticosteroid: +11; 5 patients on glucocorticosteroid + ASA with disease in colon +9 and 7 patients on glucocorticosteroid + ASA with disease not confined to colon +11. All patients on elemental diet: + 11; 4 patients on elemental diet with disease confined to colon + 9; 8 patients on elemental diet with disease not confined to colon +11.			NA			
Mean height velocity			1		Mean height velocity standard deviation score estimated for 6 months after treatment was -3.1 in the glucocorticosteroid + ASA group and + 0.32 in the elemental diet group ($p < 0.05$)			NA			

1.4.2 Maintaining remission

1.4.2.1 Half enteral nutrition versus free diet for maintaining remission

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 6531 Takagi et al, 2006[68] Country: Japan	RCT	51patients	Inclusion: Patients who had just undergone induction of remission (CDAI < 150) by either EN, TPN, prednisolone or infliximab. Exclusion: CDAI > 150 Demographic comparison: NSD in gender, age (all adult), BMI, disease site, inductive therapy, mean CDAI, use of azathioprine.	Group 1: Half EN took half their daily calories (900-1200) by EN (NG tube or oral) and remaining half by usual unrestricted meals. Food diaries were kept by both groups. Mesalazine (2250-3000 mg/day) was taken by all patients.	Group 2: Free diet group took all nutrients via usual unrestricted meals	1 year	Relapse rates Adverse events	See effect size table	No external funding	Oral or via self-inserted nasogastric tube

Effect Size			
Outcome	Number of patients	Treatment vs. control Hazard Ratio (95% CI)	Notes
Relapse rate (mean follow-up 11.9 months)	9/26 Half EN 16/25 Free diet	Multivariate HR (95% CI)[Adjusted for age, sex, duration of disease, disease site and mean CDAI at baseline]: 0.40 (0.16 to 0.98) Half EN; 1.00 (referent) Free diet	Interim analyses were scheduled semi-annually. At the fourth analysis, after 51 patients had been assigned, the trial was stopped (sample size calculations required 65 patients per group) because the relapse rate in the half EN group was significantly lower than that in the free diet group.

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Adverse events		25		0 events			No adverse events such as severe symptoms because of an excessive calorie intake, high osmotic pressure diarrhoea caused by EN, or instrumental trouble related to the feeding tube in the half EN group, occurred in any patient.			

1.4.2.2 Observational studies for enteral nutrition maintaining remission

The evidence table for Verma 2001[69] (see '3. Clinical methodological introduction') is presented below. Further evidence tables below summarise data for three prospective non randomised studies[70-72] and one retrospective chart review[73] of enteral nutrition for maintenance of remission of Crohn's disease.

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up
Ref ID: 546 Verma , 2001[69] Country: UK	Cohort data from RCT	33 adult patients	Inclusion: Patients with inactive CD (CDAI = 150 in the 2 weeks preceding the study) and ESR < 20 mm/h; previously documented glucocorticosteroid-dependency Patients taking AZA/MP or 5-ASA were included provided they were glucocorticosteroid-dependent. Exclusion: CDAI > 150 Demographic comparison: The patient population comprised 10 males and 23 females. The mean age was 40.8 + 2.7. Mean dose of prednisolone at entry was 7.0 + 0.5 and patients had been taking glucocorticosteroid for a mean of 46.7 + 11 months. 14 patients were taking AZA and 5 were taking 5-ASA. No statistically significant differences were evident with regard to age, disease duration, length of remission prior to entry, dose of glucocorticosteroid, disease location or number of previous unsuccessful attempts to withdraw glucocorticosteroid.	Group 1: Elemental diet	Group 2: Polymeric diet	1 year

Effect Size			
Outcome	Number of patients	Results	
Maintenance of remission without glucocorticosteroid at one year	33 randomized patients	27/33 (82%) patients overall tolerated the nutritional supplement (13 elemental and 14 polymeric) 14/33 (42%) of patients randomised to EN vs. 19/33 (58%) of patients randomised to normal diet remained in remission for 12 months after complete withdrawal of glucocorticosteroid.	RR 0.74 (0.45 to 1.21)

Author Country	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Hirakawa et al, 1993[70] Country: Japan	Prospective open label non-randomised trial	61 adult patients with Crohn's disease in remission	Not described	Total enteral nutrition, Elental (25 patients) EN for remission was used in conjunction with low fat, low residue and low meat oral diet	Enteral nutrition and drugs (i.e. prednisolone 0.75 mg/kg/day for those with small bowel lesions and sulfasalazine 3-4 g/day for those with large bowel lesions (22 patients); OR, Drug treatment alone (8 patients); OR, no maintenance therapy (6 patients)	1, 2 and 4 years	Remission defined according to the International Organization for the study of Inflammatory Bowel Disease (IOIBD) score and normalization of ESR and CRP	Cumulative continuous remission rates after one, 2 and 4 years: EN group: 94%, 63% and 63% respectively; EN + drug group 75%, 66% and 66% respectively; Drug only group 63%, 42% and 0% respectively; No maintenance therapy 50%, 33% and 0% respectively. When more than 30 kcal/kg ideal body weight/day of the EN was given (n = 31), maintenance of remission was successful in 95% patients.	Not stated
Outcome		Number of Patients		Results					
Remission EN vs. no treatment at one year		24/25 (96%)	3/6 (50%)	RR 1.92 (0.86 to 4.29)					
Remission EN + drugs vs. no treatment at one year		19/25 (76%)	3/6 (50%)	RR 1.52 (0.663.49)					

Author Country	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of Funding
Verma et al, 2000[71] Country: UK	Prospective open label non-randomised trial	39 adult patients with Crohn's disease in remission	Included: Patients with CDAI < 150 There was NSD with regard to disease site, dose and duration of pre-trial medication, concurrent medication, CDAI, CRP and body mass index. There was a female preponderance in both groups (male to female ratios for nutritional supplement 7:14; normal food 5:13). Patients who elected to take normal un-supplemented diet had a longer disease duration 91+ 14.8months vs.60 +14.8months) and had been on glucocorticosteroid for a shorter time (7.4 + 3.2months vs. 16.8 +. 9months)	Elemental diet EO28 Extra as supplement to normal diet (Group 1, n = 21 patients) Patients in both groups were weaned off prednisolone over 4-6 weeks, and AZA and 5-ASA preparations were continued throughout the study	Normal diet (Group 2 18 patients)	12 months	Treatment failure as defined by increase in CDAI by more than 100 points from baseline or a final CDAI > 150; or need for surgery; or requirement of increasing doses of glucocorticosteroid to more than 20 mg daily.	A total of 17 patients (81%) tolerated the nutritional supplementation. On an ITT basis, 10/21 patients (48%) remained in remission for 12 months, compared to 4/18 (22%) patients on normal diet, p < 0.0003. Seven patients in Group 1 and 14 in Group 2 relapsed at a mean of 7.4 + 0.9 and 6.2 + 0.4 months respectively.	Not stated
Remission				10/21 (47.6%)	4/18 (22.2%)		RR 2.14 (0.81 to 5.67)		

Author Country	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Wilschanski et al, 1996[73] Country : Canada	Retrospective chart review	47 children with Crohn's disease who achieved remission on exclusive nasogastric tube feeding of an elemental or semi-elemental liquid diet	Not described for the cohort in remission.	Children who continued nocturnal EN to supplement normal ad lib daytime diet	Children on normal diet only without supplement	1 year	Remission as measured by PCDAI < 20, as well as ESR and albumin levels. Height velocity	Relapse rates at 12 months (15/19 no supplement vs. 12/28 with EN supplements) (log rank [comparison of survival distributions] p = 0.005) Indicates a significant difference in favour of EN supplementation. Mean height velocity of 24 eligible patients receiving supplementation with complete before and after treatment data was greater during the treatment year (6.1 [4.2 cm]) than during the previous year (3.2 [1.6 cm]) (p < 0.001). For the seven non-supplemented patients with complete before and after treatment measurements, the mean height velocity during the second year (4.2 [4.5 cm]) did not differ significantly from that recorded during the previous year (3.8 [1.2 cm]). Comparing paired data between the two cohorts, the mean change in height velocity was 2.87 cm/year among those continuing supplements versus 0.4 cm/year among those who did not (p = 0.057).	
Outcome		Number of Patients		Results					
Relapse		12/28 (42.9%)EN vs. 15/19 (78.9%) normal diet		0.54 (0.33 to 0.88)					

Author Country	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Source of funding
Yamamoto et al, 2007[72] Country: Japan	Prospective non-randomised cohort study	40 adult patients with CD who achieved clinical remission	Inclusion: CD patients aged between 15-75 years; in clinical remission for < 8 weeks. All patients in both groups received Pentasa 3000 mg/day as a prophylactic medication during the study. No patient received glucocorticosteroid treatment, immunosuppressive drugs or infliximab except patients who relapsed.	Continuous elemental diet (Elental)infusion at night and low fat diet during the daytime	No treatment	1 year	Clinical relapse CDAI > 150.	The cumulative proportion of patients in remission in the EN and the non-EN groups during the 1-year study period: the outcome in the EN group was significantly better than the no treatment group (p = 0.01 by the log rank test)	Not stated
Outcome		Number of Patients		Results					
Remission		40 patients		EN group significantly better than non-EN group at one year p = 0.01 by log rank test					

1.4.2.3 Economic evidence table – half enteral nutrition for maintaining remission

Quality of life of patients and medical cost of "half elemental diet" as maintenance therapy for Crohn's disease: Secondary outcomes of a randomised controlled trial, Takagi, S.; Utsunomiya, K.; Kuriyama, S.; Yokoyama, H.; Takahashi, S.; Umemura, K.; Iwabuchi, M.; Takahashi, H.; Takahashi, S.; Kinouchi,Y.; Hiwatashi, N.; Funayama, Y.; Sasaki, I.; Tsuji, I.; Shimosegawa, T., Disease and Liver Disease 2009, 41: 390-394

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CCA **Study design:** Within RCT analysis **Perspective:** Japanese medical system **Time horizon:** 2 years **Treatment effect duration:** 2 years **Discounting:** Costs: No; Outcomes: No	**Population:** Patients with Crohn's disease who are in remission **Cohort settings:** Mean age = 31 years Male/Female = men ≥ 70% **Intervention 1:** Half elemental diet (Elental®) **Intervention 2:** Free diet	**Total costs (mean per patient per month):** Half elemental diet: 1. Crude costs: ¥109,160 (£611); 2. Adjusted costs: ¥105,860 (£593)*** Free diet: 1. Crude estimate: ¥68,970 (£386); 2. Adjusted costs: ¥72,400 (£405)*** Incremental (1-2): £188 = 5412 over 2 years (adjusted) 95%CI, ; p = NR No statistical difference in monthly mean costs between the interventions **Currency & cost year:** 2009 Japanese Yen presented here as 2009 UK pounds‡ **Cost components incorporated:** Half-elemental diet (dietary costs of free-diet group not considered as a medical expense); costs of additional treatments and hospitalizations for relapse	**Primary outcome measure:** Cumulative probability of relapse at 2 years Half-elemental diet: 35% Free diet: 64% Hazard ratio: 0.4 (95% CI: 0.16 to 0.98) Incremental (2-1): 0.29 relapses per patient (CI , ; p = not reported) **Other outcome measures (mean):** IBDQ QoL score (at 1 and 13 months after start of treatment) Half elemental diet: 1. Crude IBDQ scores: 165 and 179 2. Adjusted IBDQ scores: 167 and 172*** Free diet: 1. Crude IBDQ scores: 171.5 and 171.9 2. Adjusted IBDQ scores; 169 and 177*** No statistical difference in QoL between the interventions (p = NR)	**Primary ICER:** ICER: £15,600 per relapse prevented CI: N/A Probability cost-effective: N/A **Analysis of uncertainty:** Precision around estimates of costs and quality of life (presented as confidence intervals) but not around incremental cost or cost-effectiveness
Data sources				

Quality of life of patients and medical cost of "half elemental diet" as maintenance therapy for Crohn's disease: Secondary outcomes of a randomised controlled trial, Takagi, S.; Utsunomiya, K.; Kuriyama, S.; Yokoyama, H.; Takahashi, S.; Umemura, K.; Iwabuchi, M.; Takahashi, H.; Takahashi, S.; Kinouchi,Y.; Hiwatashi, N.; Funayama, Y.; Sasaki, I.; Tsuji, I.; Shimosegawa, T., Disease and Liver Disease 2009, 41: 390-394
Health outcomes: Estimated from a randomized controlled trial (Takagi et al. 2006)[68]. **Quality-of-life weights:** Estimated from the RCT above using the McMaster Inflammatory Bowel Disease Questionnaire (IBDQ), which was translated into Japanese **Cost sources:** Japanese healthcare costs.
Comments
Source of funding: None; **Limitations:** It is not clear whether all important and relevant costs were included in the study, and for the costs included, it is not clear as to whether these are real resource costs or [public insurance] charges. The trial was stopped early due to the observed treatment effect.
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

*Abbreviations: CCA = cost-consequence analysis; CI = confidence interval; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 2009 Purchasing Power Parities [http://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP] * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious Limitations/Very serious limitations ***Adjusted for baseline characteristics (age, sex, duration of disease, disease site, perianal lesions, previous gut operation, frequency of relapse, administration of azathioprine, inductive therapy (+ surgery) and mean Crohn's Disease Activity Index [CDAI] at baseline)*

1.5 Surgery

1.5.1 Surgery limited to the distal ileum versus medical management

1.5.1.1 Surgery versus medical management – paediatric study

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 827 Singh Ranger et al, 2006[74] Country: UK	Retrospective case study		8	Inclusion: Children < 16 years with CD who failed medical treatment Demographic comparison: Age range 10.8 to 14.9 years	Surgery	Medical treatment	6 months	Growth velocities glucocorticosteroid-treated recurrence Surgically treated recurrence HBI scores	See effect size table	Not stated	NA

Effect Size			
Outcome	Number of patients	Pre-operative vs post-operative	
Height velocities	8	Mean height velocity (cm/month) 0.15 vs. 0.54	Velocity change + 0.39 (SD 0.28) p = 0.006
Weight velocities	8	Mean weight velocity (kg/month) 0.15 vs. 0.59	Velocity change 0.44 (SD 0.88) p = 0.19
HBI	8	Mean HBI score 2.00 (0.58) vs. 0.84 (0.75)	p = 0.003

1.5.1.2 Surgery vs medical management – adult study

Bibliographic reference	Study type		Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration
Ref ID: 710 Sayfan et al[75] Country: Israel	Prospective cohort		34	Inclusion: 22 patients who underwent surgery for CD and 12 patients who were admitted to hospital during the study period for medical treatment due to exacerbation of their disease Demographic comparison: There were 15 males (68%) and seven females (32%) in the surgical group and seven males (58%) and five females (42%) in the medical group. The median age in these groups was 33 years (14-85) and 35 years (18-83) respectively. Sixteen patients (73%) were operated on electively and six (27%) had emergency surgery. In the surgical group, 16 patients (73%) were on prolonged steroid treatment at the time of operation. In the	Surgery	Medical treatment	16 months	Hospital admissions; Chronic corticosteroids intake; Life quality by questionnaire CDAI score	See effect size table		NA

				medical group the corresponding number at the time of enrolment into the study was eight patients (66%).							
Effect Size											
Outcome	Number of patients	Medical vs. surgical									
Hospital admissions	12 medical; 22 surgical	5 medical (40%) vs. 1 surgical (4.5%)									RR 9.17 (1.21 to 69.69)
Weaned off chronic glucocorticosteroid use	8 medical; 16 surgical	None (0) in medical group vs. 10/16 (62.5%) in surgical group weaned off									RR 0.09 (0.01 to 1.36)
Improved quality of life by questionnaire	12 medical; 22 surgical	All patients who had surgery reported improvement in the quality of life according to the Irvine et al questionnaire and subjective relief of symptoms. There was no change in the group treated medically only.									RR 0.04 (0.00 to 0.60)
CDAI score	12 medical; 22 surgical	Mean CDAI score in the surgical group was 7 (SD 3.0299) before the operation and 5 (SD 3.1623) post-op.* In the medical group the mean CDAI score was 5 (SD 3.1533) at enrolment and remained so for the duration of the study. *									P < 0.05

1.5.1.3 Recurrence rates for elective surgery of terminal ileum after first resection

In view of the paucity of evidence for this question, it was considered that data regarding the clinical, surgical and mucosal recurrence rates for elective surgery of the terminal ileum would be useful information for discussion with patients. The data was obtained from observational reviews of greater than 20 patients.

Author	Sample size	Length of follow-up (median)	Overall recurrence rate	Clinical recurrence rate	Surgical recurrence rate	Mucosal recurrence rate	Quality of Life
Agrez, 1982[76]	23 with small and large bowel disease	8.5 years	48%				
Andrews, 1991[77]	139 distal ileal disease	10 years	79%		58%		
Baldassano, 2001[78]	39 ileocaecal disease	4.4	36%				
Chardavoyne, 1986[79]	37 with small and large bowel disease	10 years			35%		
Cook, 2007[80]	37 (32 with follow up information) children with ileo-caecal disease	3.8 years			28%		
Dirks, 1989[81]	58 patients with ileocolitis	4 years			20%		
Eshuis, 2010[82]	55 with ileocaecal disease	6.8 years		38%	9%		
Hellers, 1979[83]	277 with ileocaecal disease	5 years 10 years 15 years	30% 50% 55%				
Kirkegaard, 1978[84]	20 with CD of terminal ileum	5 years	40%		30%		
Ng, 2009[85]	99 with ileocaecal disease	1 year		28%	5%		
Scarpa, 2007[86]	97 with ileocolonic resection	47.1 months					Normal on CGQL*; impaired on HRQL **and

							PIBDQL**
Stocchi, 2008[87]	56	10.5 years	52%		28.5%		
Author	Sample size	Length of follow-up (median)	Overall recurrence rate	Clinical recurrence rate	Surgical recurrence rate	Mucosal recurrence rate	Quality of Life
			Range 30-79%	Range 28-38%	Range 5-58%		Normal on CGQL*; impaired on HRQL **and PIBDQL**

**Cleveland Global Quality of Life; ** Health Related Quality of Life; ***Padova Inflammatory Bowel Disease Quality of Life*

1.5.2 Stricture management

1.5.2.1 Efficacy and safety of balloon dilatation (NR - not reported)

Author Country	Study Period	No. of CD patients ITT	Average (mean) follow-up (months)	Success rate patients (%)	Major Complications (%)*	Need for re-intervention (%) in total sample	Need for re-intervention (%) in successfully dilated sample	Stricture recurrence (%)	Need for surgery (%) in total sample	Need for surgery (%) in successfully dilated sample	Quality of life
Dear et al[88] UK	1992-1999	22	45	22/22 (100)	0/22 (0)	10/22 (45.5)	NR**	NR	6/22 (27.3)	NR	NR
Fukumoto et al[89] Japan	2000-2005	23	11.9	17/23 (73.99)	0/23 (0)	NR	4/23 (17)	NR	NR	2/23 (8.6)	NR
Foster et al[90] USA	1996-2005	24 Glucocorticosteroid use to augment procedure In 14 of 24 people (58.6%)	25.6	24/24 (100)	2/24 (8)	13/24 (54.2)	NR	NR	2/24 (8.3)	NR	NR
Hirai et al[91] Japan	2005-2007	25	6	18/25 (72)	1/25 (4)	6/25 (22.2)	NR	NR	5/25 (20)	NR	NR
Stienecker et al[92] Germany	1997-2007	25	81	20/25 (80)	1/25 (4)	7/25 (28)	NR	NR	4/25 (16)	NR	NR
Hoffman et al[93] Germany	2001-2006	27	17	25/27 (92.6)	1/27 (4)	NR	13/27 (48)		6/27 (24)	6/27 (24 overall) 4/27 (16 due to stricture)	NR
Blomberg et al [94] Sweden	1987-1989	27	19	27/27 (100 with temporary effect)	4/27 (14)	4/27 (14)	NR	33	8/27 (29.6)		NR

Author Country	Study Period	No. of CD patients ITT	Average (mean) follow-up (months)	Success rate patients (%)	Major Complications (%)*	Need for re-intervention (%) in total sample	Need for re-intervention (%) in successfully dilated sample	Stricture recurrence (%)	Need for surgery (%) in total sample	Need for surgery (%) in successfully dilated sample	Quality of life
Nguyen-Tang et al[95] Switzerland	1996-2004	27 (Survey response rate 87%)	47	NR	NR	NR	NR	NR	NR	NR	GIQLI Health related quality of life was significantly impaired in balloon dilatation patients vs. surgical controls and healthy participants (p = 0.005). Impaired categories included GI symptoms (p < 0.001) and stress by treatment (p < 0.05).
Ajlouni et al[96]	1993-	37	29 (median)	31/37	1/37 (3)	8/37 (22)	10/37 (26)	26	4/37 (12)	2/37 (6.5)	NR

Author Country	Study Period	No. of CD patients ITT	Average (mean) follow-up (months)	Success rate patients (%)	Major Complications (%)*	Need for re-intervention (%) in total sample	Need for re-intervention (%) in successfully dilated sample	Stricture recurrence (%)	Need for surgery (%) in total sample	Need for surgery (%) in successfully dilated sample	Quality of life
Australia	2005			(84)							
Sabate et al [97] France	1991-2000	38	22.8	32/38 (84)	1/38 (2)	NR	14/38 (37.5)	36 at 1 year 44 at 2 years 60 at 5 years	15/38 (39.5)	10/38 (26 at 1 year) 14/38 (38 at 2 years) 16/38 (43 at 5 years)	NR
Morini et al[98] Italy	1988-2001	43	63.7	33/43 (76)	0/43 (0)	31/43 (72.1)	28/43 (64.7)	NR	NR	20/43 (47)	NR
Ferlitsch et al [99] Austria	1993-2003	46	21 (median)	39/46 (84)	4/46 (7.6)	NR	14/46 (31)			13/46 (28 resection) 1/46 (3 stent)	NR
Couckuyt et al [100] Belgium	1989-1992	55	33.6		6/55 (11)	35/55 (63.6)	NR	NR	19/55 (34.5)	NR	NR
Matsui et al[101] Japan	1989-1999	55	37	46/55 (83)	1/55 (1.8)	30/55 (55)	30/55 (55)	NR	NR	12/55 (22.5)	NR
Muller et al[102] Germany	1999-2008	55	44	52/55 (95)	1/55 (1.8)	26/55 (47)	NR	NR	13/55 (24)	NR	NR
Thomas-Gibson et al[103] UK	1983-1999	59	29.4 (median)	53/59 (82)	2/59 (3)	48/59 (81)	NR	NR	35/59 (59)	NR	NR
Matsui et al[104] Japan	1992-2002	60	55.2	50/60 (83.3)	2/60 (3.3)	NR	NR	NR	NR	19/60 (32)	NR
Blomberg[105] Sweden	1967-1992	73	Not stated	63/73 (86)	9/73 (12)	NR	NR	NR	NR	NR	NR
Van Assche et al[106]	1995-2006	138	69.6	134/138 (97)	7/138 (5)	63/138 (46)	NR	NR	33/138 (24)	NR	NR

Author Country	Study Period	No. of CD patients ITT	Average (mean) follow-up (months)	Success rate patients (%)	Major Complications (%)*	Need for re-intervention (%) in total sample	Need for re-intervention (%) in successfully dilated sample	Stricture recurrence (%)	Need for surgery (%) in total sample	Need for surgery (%) in successfully dilated sample	Quality of life
Belgium											
Summary		859		686/777 88.3%	43/832 5.2%	281/565 49.7%	137/278 49.3%	34% at mean ≤ 3 years; 40% at mean ≤ 5 years	150/632 23.7%	72/269 27% at mean ≤ 5 years	N/A

1.5.2.2 Time to recurrence – balloon dilatation (NR-not reported)

Study	Time to recurrence	Time to reoperation
Ajlouni (2006)[96]	NR	Median time to recurrent symptomatic stricture requiring dilation or surgery 8 months (7-112 months)
Blomberg (1992)[105]	Symptom relief 'lasting from a few days to well over two years'	NR
Blomberg (1991)[94]	NR	NR
Couckuyt (1995)[100]	Data presented as Kaplan-Meier curve – 50% remained symptom free at 16 months. At 5 years 30% were symptom-free.	Second dilation mean time interval of 1.5 years
Gevers (1994)[107]	NR	NR
Dear (2001)[88]	NR	NR
Ferlitsch (2006)[99]	NR	Median 6 months (1-98)
Foster (2008)[90]	NR	Median time between dilations 3 months (1-40 months)
Fukumoto (2007)[89]	NR	NR
Hirai (2010)[91]	NR	Mean time to surgery 10.4 months after dilation
Hoffmann (2008)[93]	NR	Median time to re-dilation 11 months (2-38 months)
Matsui (2004)[104]	NR	NR
Matsui (2000)[101]	NR	NR
Morini (2003)[98]	Median symptomatic relief 88 months (20-168)	Median interval between first dilation and surgical procedure 21.5 months (10-142 months)
Mueller (2009)[102]	NR	Median time to surgery 1.5 months (0-20 months)
Nguyen-Tang (2008)[95]	NR	NR
Sabate (2003)[97]	Data presented as Kaplan-Meier curve – 50% remained symptom-free at 29 months; 36% remained symptom-free at 5 years.	Median interval between first and second dilations 4.7 months (1-14 months)
Stienecker (2009)[92]	Mean stricture relapse time after successful dilation 32 months (3-77 months)	NR

Study	Time to recurrence	Time to reoperation
Thomas-Gibson (2003)[103]	NR	Median time to surgery 4.9 months post-dilation
Van Assche (2010)[106]	NR	Median time to new dilation or surgery after first dilation 12.5 months (6-21.5 months)

1.5.2.3 Efficacy of surgical treatment for stricture (NR – not reported)

Study	Study period	No of patients	Median* or mean follow-up (mo)	Site of Surgery (includes multiple surgeries for stricture in study population)				Symptomatic recurrence	Reoperation for recurrence
				Jejunum/ Ileum	Previous anastomosis	Duodenum	Large bowel		
Quandalle et al. (1994)[108] Lille, France	1985-1991	22	36 (12-90)	103	2	2	0	9/22	5/22
Michelassi & Upadhyay (2004)[109] Chicago, USA	1992-2003	30	N/A	28	0	0	3	N/A	7/30
Tonelli et al. (2004)[110] Florence, Italy	1996-2002	31	28 (3-74)	87	0	0	0	N/A	6/31
Spencer et al. (1994)[111] Mayo, USA	1985-1991	35	36	NR	NR	NR	NR	7/35	6/35
Serra et al. (1995)[112] Toronto, Canada	1985-1994	43	54.5 (4-108)	149	3	2	0	17/43	14/43
Yamamoto et al. (1999)[113] Birmingham, UK	1980-1997	111	107*(3-206)	258	27	0	0	20/111	10/111
Tonelli & Ficari (2000)[114] Florence, Italy	1981-1996	44	50	166	7	1	0	N/A	7/44
Hurst & Michelassi (1998)[115] Chicago, USA	1989-1997	57	38 (3-95)	99	9	0	1	N/A	16/57
Broering et al. (2001)[116] Hamburg, Germany	1987-1996	58	70*	0	21	0	52	N/A	24/58
Broering et al. (2001)[117] Hamburg, Germany	1987-1996	67	53* (12-118) 106* (12-126)	103	12	4	0	18/67	13/67
Baba & Nakai (1995) [118] Multi-centre, Japan	N/A	69	37 (0-133)	NR	NR	NR	NR	N/A	18/69
Greenstein et al. (2009)[119] New York, USA	1984-2004	88	82.8	315	10	0	14	N/A	52/88
Fearnhead et al. (2006)[120] Oxford, UK	1978-2003	100	85.1	477	0	0	2	N/A	45/100

Study	Study period	No of patients	Median* or mean follow-up (mo)	Site of Surgery (includes multiple surgeries for stricture in study population)				Symptomatic recurrence	Reoperation for recurrence
Futami & Arima (2005)[121] Fukuoaka, Japan	1989-2002	103	80.3 (12-187)	271	11	2	4	60/103	49/103
Dietz et al. (2001)[122] Cleveland, USA	1984-1999	314	90*	1096	28	0	0	N/A	116/314
Sampietro et al. (2009)[123] Milan, Italy	1993-2007	393	62 (23-101)	327	0	66	0	N/A	67/393
Study	Study period	No of patients	Median* or Mean Follow-up (mo)	Site of Surgery				Symptomatic recurrence	Reoperation for recurrence
				Jejunum/ Ileum	Previous Anastomosis	Duodenum	Large bowel		
Totals		**1565**	**0-206 months**	**3479**	**130**	**77**	**76**	**131/381 (34%)**	**455/1565 (29%)**

1.5.2.4 Safety of surgery for stricture – complications

Study	Study period	No of patients	Overall complications	Sepsis (fistula, abscess, leak)	Haemorrhage*	Ileus	Wound infection	Obstruction	Other	Mortality
Quandalle et al. (1994)[108] Lille	1985-1991	22	1	1	0	0	0	0	0	0
Michelassi & Upadhyay (2004)[109] Chicago	1992-2003	30	3	1	1	0	0	0	0	1
Tonelli et al. (2004)[110] Florence	1996-2002	31	6	0	1	0	0	0	5	0
Spencer et al. (1994)[111] Mayo	1985-1991	35	5	0	0	0	2	2	1	0
Serra et al. (1995)[112] Toronto	1985-1994	43	7	1	1	0	5	0	0	0
Tonelli & Ficari (2000)[114] Florence	1981-1996	44	3	0	1	0	0	2	0	0
Hurst & Michelassi (1998)[115] Chicago	1989-1997	57	7	1	1	2	0	3	0	0
Broering et al. (2001)[116] Hamburg	1987-1996	58	13	2	2	1	4	2	2	0
Broering et al. (2001)[117] Hamburg	1987-1996	67	12	0	6	0	5	1	0	0
Baba & Nakai (1995)[118] Japan	N/A	69	3	1	0	0	1	1	0	0
Greenstein et al. (2009)[119] New York	1984-2004	88	9	2	0	3	4	0	0	0
Fearnhead et al. (2006)[120] Oxford	1978-2003	100	27	11	4	0	0	4	5	3
Futami & Arima (2005)[121] Fukuoka, Japan	1989-2002	103	11	7	1	2	0	0	1	0
Yamamoto et al. (1999)[124] Birmingham	1980-1997	111	24	8	2	4	6	0	4	0
Dietz et al. (2001)[122]	1984-	314	57	13	23	14	4	3	0	0

Study	Study period	No of patients	Overall complications	Sepsis (fistula, abscess, leak)	Haemorrhage*	Ileus	Wound infection	Obstruction	Other	Mortality
Cleveland	1999									
Sampietro et al. (2009)[123] Milan	1993-2007	393	22	15	5	2	0	0	0	0
Study	Study period	No of patients	Overall complications	Sepsis (fistula, abscess, leak)	Haemorrhage*	Ileus	Wound infection	Obstruction	Other	Mortality
Totals		1565	210/1565 (13%)	63/1565 (4%)	48/1565 (3%)	28/1565 (1.8%)	31/1565 (2%)	18/1565 (1%)	18/1565 (1%)	4/1565 (0.26%)

1.5.2.5 Time to recurrence – surgery for stricture (NR – not reported)

Study	Time to recurrence	Time to reoperation
Baba (1995)[118]	NR	NR
Broering (2001) [116] – large bowel	Mean time to recurrence after strictureplasty 26.6 months, after resection 33.5 months	NR
Broering (2001) [117] – small bowel	Mean time to recurrence after strictureplasty 16 ± 14 months, after resection 34 ± 19 months	NR
Di Abriola (2003)[125]	NR	NR
Dietz (2001)[122]	NR	Data presented as Kaplan-Meier curve – 20% reoperation at 5 years; 50% reoperation at 10 years
Fearnhead (2006)[120]	NR	Mean time to reoperation 34.3 months (0.2-205.8 months)
Futami (2005)[121]	NR	Data presented as Kaplan-Meier curve – 45% reoperation at 5 years; 62 % reoperation at 10 years.
Greenstein (2008)[119]	NR	20 % (CI 12-28%)at 5 years and 38% (CI 26-50%)at 10 years
Hurst (1998)[126]	NR	Mean time to surgical recurrence 30 months (10-67 months)
Michelassi (2004)[109]	NR	Mean time to reoperation 53 months (13-98 months)
Oliva (1994)[127]	Mean time to exacerbation 7.5 months	NR
Quandalle (1994)[108]	Median time to symptomatic recurrence 24 months (6-36 months)	NR
Sampietro (2009)[123]	17.1% at 5 years; 33.5% at 10 years	NR
Serra (1995)[112]	NR	Mean time to second surgery 2.4 years
Spencer (1994)[111]	NR	Mean time to re-exploration for obstruction 2.2 years (9 months-3.5 years)
Tonelli (2004)[110]	NR	Mean time to reoperation 44 months (13-60 months)

1.5.2.6 Quality of life after strictureplasty verses resection: IBDQ

Study	Study period	No of patients	Median follow-up (mo)	Bowel (7-70 points)	Systemic symptoms (5-35 points)	Emotional function (12-84 points)	Social function (5-35 points)	Total/maximum points
Broering et al. (2001) (large bowel)	1987-1996	Strictureplasty = 17 Resection = 25	70 70.5	50 (33-68) 53 (37-70)	24 (12-35) 27 (15-35)	69 (37-84) 69 (31-84)	34 (6-35) 33 (11-35)	177/224 182/224
Broering et al. (2001) (small bowel)	1987-1996	Strictureplasty = 18 Resection = 32	53 (12-118) 106 (12-126)	50 (19-70) 56 (32-70)	24 (7-35) 26 (11-35)	64 (24-84) 67 (31-84)	28 (11-35) 30 (18-35)	167/224 181/224

1.5.2.7 Paediatric stricture surgery studies

Study	Study period	No of patients	Median or Mean age at surgery	Median* or mean follow-up (mo)	Site of surgery				Early/late complications	Weaned from glucocortico-steroids	Change in PCDAI
					Jejunum/Ileum	Previous anastomosis	Duodenum	Large bowel			
Oliva et al. (1994)[127]	1987-1992	8	Mean age 16 (10-19)	19 (3-55)	NR	NR	NR	NR	2 (haemorrhage)	83%	NR
Di Abriola et al. (2003)[125]	N/A	5	Mean age 16 (14-20)	22 (6-30)	5	0	0	0	0	100%	-42.5

1.6 Monitoring

1.6.1 Osteopenia

1.6.1.1 Fracture risk in children

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration	Comments
Ref ID: 20567 Kappelman et al, 2011[128] Country: USA	Case control	733 Children (less than 20 years) with CD and 3287 controls.	Inclusion: Cases were identified using administrative data from 87 health plans in 33 states. Each case was matched to three controls on the basis of age, gender and geographical region. Fractures were identified in cases and controls using ICD-9 diagnosis codes and measured oral steroid exposure using NDC (National drug codes). Demographic characteristics of total sample:	Incidence of fracture in paediatric patients with Crohn's disease	Incidence of fracture in the control group	Cross sectional study, analyzing the in-patient and outpatient insurance claims contained within the PharMetrics Patient-Centric Database for the two- year period January 1, 2003 through December 31, 2004.	Incidence of fracture	See table below	National Center for Research Resources Grant and the National Institute for Diabetes and Digestive and Kidney Diseases grants	NA	

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Route of administration	Comments
			Mean age cases 15 (3.2) years; controls 15 (3.4) years. 44% male and 44% female								

Effect Size			
Outcome	Crude incidence of fracture Case (CD) vs. Control	Prevalence per 100,000 Case (CD) vs. Control	OR (95% CI)
Any fracture	60 vs. 200	8141 vs. 10,015	0.8 (0.6 to 1.1)
Multiple fractures	11 vs. 35	1493 vs. 1753	0.8 (0.4 to 1.7)
Fracture + glucocorticosteroid prescriptions (total IBD population)	Patients with fractures had a mean of 1.6 (SD 3.5) prescriptions/year for oral glucocorticosteroid treatment vs. mean of 1.8 (SD 3.6) in patients without fracture, p = 0.6		

1.6.2 Early relapse

1.6.2.1 Faecal calprotectin

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20420 D'Inca et al., 2008[129] Country: Italy	Nested case control	65 CD patients	Inclusion: Clinical remission (CDAI ≤ 150) for at least 3 months Demographic characteristics of CD sample: 33 male; 32 female Mean age: 43 years (18-77) Median CDAI 61 (20 to 149) 46 on 5-ASA; 11 on immunosuppressant's; 8 on no therapy 16 had prior surgery Mean time in remission 17 months ± 15	Faecal calprotectin in relapsed patients (relapse CDAI > 150, with an increment of more than 50 points over the baseline)	Faecal calprotectin in non-relapsed patients	1 year	Median calprotectin concentration in mg/kg Median ESR; Median CRP	See below	Not stated	

Outcome	Comparison Relapse vs. no relapse	Outcome
Median calprotectin concentration mg/kg	207 mg/kg (95% CI 96 to 460, range 14 to 1846) vs. 88 mg/kg (95% CI 47 to 130, range 6 to 579)	p = 0.055
Median ESR mm/hour	25 mm/h (95% CI 20 to 36, range 4 to 54) vs. 15 mm/h (95% CI 12 to 23, range 2 to 51)	p = 0.055
Median CRP mg/L	5.49 mg/L (95% CI 3.82 to 6.84, range 1 to 10) vs. 3.13 mg/l (95% CI 2.38 to 8.27, range 0 to 34)	p = 0.05

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20376 Garcia-Sanchez et al., 2010[130] Country: Spain	Nested case control	66 CD patients	Inclusion: Clinical remission (CDAI < 150) for at least 3 months Demographic characteristics of CD sample: 54.4% male; 45.5% female Mean age: 36.9 years ± 9.2 22.7% smoker; 77.3% non-smoker Mean CDAI 71.1 ± 20.8 54% on mesalazine; 59% on AZA or MTX; 6% on biological treatments 33% had prior surgery Mean time in remission 17 months ± 15	Faecal calprotectin in relapsed patients	Faecal calprotectin in non-relapsed patients	1 year	Median calprotectin concentration in µg/g Mean ESR; Mean CRP	See below	Not stated	

Outcome	Comparison Relapse vs. no relapse	Results
Median calprotectin concentration µg/g	444 µg/g (95% CI 34 to 983, range 34 to 983) vs. 112 µg/g (95% CI 22 to 996, range 19 to 1150)	p < 0.01
Mean ESR mm/h	17.5 mm/h ± 11 vs. 16.2 mm/h ± 8	MD 1.30 [-5.32 to 7.92]
Mean CRP mg/l	4.6 mg/l ± 5 vs. 5.6 mg/l ± 8	MD -1.00 [-4.23 to 2.23]

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20367 Gisbert et al., 2009[131] Country: Spain	Nested case control	89 CD patients	Inclusion: Clinical remission (CDAI < 150) for at least 6 months Demographic characteristics of CD sample: Not provided for CD patients alone. Data provided for all IBD patients.	Faecal calprotectin in relapsed patients (relapse CDAI > 150)	Faecal calprotectin in non-relapsed patients	1 year	Mean calprotectin concentration in µg/g	See below Mean ESR and CRP in the total relapse group (all IBD) did not differ significantly between groups (values not stated).	Not stated	

Outcome	Comparison Relapse vs. no relapse	Results
Mean Calprotectin concentration µg/g in CD patients who suffered a relapse versus those who were in remission	266 µg/g ± 158 vs. 145 µg/g ± 186	p = 0.002 MD 121.00 (25.47 to 216.53)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20428 Kallel et al., 2010[132] Country: Tunisia	Nested case control	53 CD patients	Inclusion: Clinical remission (CDAI ≤ 150) for at least 63months Demographic characteristics of CD sample: 23 males and 30 females Median age 33 years (range 15-66) 5 smokers, 9 ex-smokers and 39 non smokers. Median disease duration 35 months (range 6 to 288 months)	Faecal calprotectin in relapsed patients (relapse CDAI > 150 or an increase of more than 100 from the inclusion value and was sufficiently severe to warrant treatment)	Faecal calprotectin in non-relapsed patients	1 year	Median calprotectin concentration in µg/g	See below	Not stated	

Outcome	Comparison Relapse vs. no relapse	Results
Median calprotectin concentration µg/g	380.5 µg/g (301to 478) vs. 155µg/g (16 to 410)	p < 0.001
Median CRP mg/l	34 mg/l (range 1 to 122) vs. 4 mg/l (range 1 to 40)	p < 0.001

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20436 Tibble et al., 2000[133] Country: England & Norway	Nested case control	43 CD	Inclusion: Children with IBD (37 with UC and 43 with CD) who had been in clinical remission between 1 and 4 months Demographic characteristics of total sample: CD patients only: Sex (M/F) 21/22 Age median (IQ range) 33 (16 to 77) Treatment: Prednisolone (5 mg/day) 6 Mesalazine 43 AZA 4	Faecal calprotectin	Relapse vs. no relapse	1 year	Median calprotectin concentration in mg/L	See below	Not stated	

Outcome	Comparison Relapse vs. no relapse	Results
Median faecal calprotectin (mg/L)	122 (98 to 229) vs. 42 (31to 49)	$p < 0.0001$
Median ESR (mm/hour)	21 (8 to 35) vs. 13 (6 to 20)	$p = 0.2$
Median CPR (mg/L)	13.1 (6 to 46) vs. 9.1 (3 to 15)	$p = 0.1$

Bibliographic reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 277 Walkiewicz et al., 2008[134] Country: USA	Nested case control	44 CD clinical encounters corresponding to each stool sample	Inclusion: Children with IBD (UC and CD) Demographic characteristics of total sample: Age 8-19; gender distribution for CD group not stated.	Faecal calprotectin	CD relapse vs. non relapse	9 months	Mean calprotectin concentration in µg/g	See table below. 89% of CD patients with FC levels less than 400 µg/g remained in clinical remission.	Not stated	

Outcome	Comparison Relapse vs. no relapse	Results
Mean faecal calprotectin (µg/g)	3214 ± 2186 vs. 1373 ± 1630	MD 1841.00 (668.65 to 3013.35)

1.6.2.2 CRP

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 257 Bitton et al., 2008[135] Country: Canada	Prospective cohort	101 CD patients entered the study. 14 patients were either lost to follow up or withdrew. These patients' data were used up to time of withdrawal but it is not clear if the data was included in the relapse or no relapse group.	Inclusion: Patients with inactive CD Demographic characteristics of total sample: Patients who relapsed during the follow up and non-relapsers were similar in all baseline characteristics.	CRP >10 mg/l	CRP <10 mg/l	1 year or less if they relapsed	Relapse as time to event and defined as CDAI score > 150 or increase of more than 70 from baseline	See table below	Crohn's and Colitis Foundation of Canada	

Outcome	Comparison	Outcome
	Prognostic factor in relation to cut-off	HR in multivariate time-dependant (14-92 days prior to relapse) model
CRP mg/l: Prediction of relapse risk	CRP > 10 mg/l vs. CRP <10 mg/l	HR 1.5 (1.1 to 1.9)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 406 Consigny et al., 2006[136] Country: France	Prospective cohort	71 patients	Inclusion: Patients with CD who had achieved a medically induced clinical remission on steroids and subsequent mesalazine and who were successfully weaned off glucocorticosteroid. Demographic characteristics of total sample: Gender female 43/71 (61%) Age at inclusion 25 years (21 to 34)	CRP > 20 mg/l ESR >15 mm/h	CRP < 20 mg/l ESR <15 mm/h	12-18 months	Relapse as time to event and defined as CDAI score > 150 or increase of more than 100 from level at remission	See table below	Not stated	

Outcome	Comparison	Result
	Prognostic factor in relation to cut-off	RR using a multivariate Cox model with time-dependent covariates
CRP mg/l: Prediction of relapse risk	CRP >20 mg/l vs. CRP < 20 mg/l	RR of relapse within the next 6 weeks: 10.5 (2.3 to 48.1)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20420 D'Inca et al., 2008[129] Country: Italy	Prospective cohort	65 CD patients	Inclusion: Clinical remission (CDAI ≤ 150) for at least 3 months Demographic characteristics of CD sample: 33 male; 32 female Mean age: 43 years (18-77) Median CDAI 61 (20 to 149) 46 on 5-ASA; 11 on immunosuppressant's; 8 on no therapy 16 had prior surgery Mean time in remission 17 months ± 15	Faecal calprotectin >130 mg/kg chosen as best cut-off, with a sensitivity of 68% and specificity of 67%, a positive predictive value of 52% and negative predictive value of 79%	Faecal calprotectin <130 mg/kg	1 year	Relapse as time to event and defined as a worsening clinical picture with CDAI > 150 with an increment of more than 50 points over the baseline score.	See below	Not stated	

Outcome	Comparison of Prognostic factor in relation to cut-off	Outcome Odds ratio from multivariable analyses
CRP mg/L: Prediction of relapse risk	CRP > 6 mg/L vs. CRP < 6 mg/L	OR -0.444 (0.067 to 6.131) Made assumption that OR = B coefficient, i.e. OR = eb (Exp) OR = 0.6414

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20428 Kallel et al., 2010[132] Country: Tunisia	Prospective cohort	53 CD patients	Inclusion: Clinical remission (CDAI ≤ 150) for at least 63months Demographic characteristics of CD sample: 23 males and 30 females Median age 33 years (range 15-66) 5 smokers, 9 ex-smokers and 39 non smokers. Median disease duration 35 months (range 6 to 288 months)	Faecal calprotectin >340 mcg/g chosen as the cut-off, with a sensitivity to predict relapse of 80% and specificity of 90.7%	Faecal calprotectin < 340 mcg/g	1 year	Relapse as time to event and defined as CDAI score > 150 or increase of more than 100 from inclusion value and worsening symptoms	See below	Not stated	

Outcome	Comparison Prognostic factor in relation to cut-off	Hazard ratio from univariate and multivariable analyses Results
CRP mg/L : Prediction of relapse risk	CRP > 9 mg/L vs. < 9 mg/L	HR 7.6 (2.0-29.5) – univariate analysis HR 5.1 (95% CI 0.5-53.3) multivariate analysis

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic Factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 342 Kurer et al., 2007[137] Country: UK	Retrospective cohort	98	Inclusion: Patients who underwent an operative procedure for CD during a 10 year period (January 1995 – December 2004) Demographic characteristics of total sample: There was no significant difference between no early recurrence and early recurrence with regard to age, gender, smoking, family history.	Raised CRP	Normal CRP	36 months	Symptomatic disease that was confirmed histologically or by radiological evidence of new mucosal ulceration and/or strictures	See table below	None stated	

Outcome	Comparison of prognostic factor	Result
Normal CRP (values not given)	Raised CRP vs. normal CRP No threshold provided	RR 0.84 (95% CI 0.50 to 1.41)

1.6.2.3 ESR

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 406 Consigny et al., 2006[136] Country: France	Prospective cohort	71 patients	Inclusion: Patients with CD who had achieved a medically induced clinical remission on steroids and subsequent mesalazine and who were successfully weaned off glucocorticosteroid. Demographic characteristics of total sample: Gender female 43/71 (61%) Age at inclusion 25 years (21 to 34)	CRP > 20 mg/l ESR > 15 mm/h	CRP < 20 mg/l ESR < 15 mm/h	12-18 months	Relapse as time to event and defined as CDAI score > 150 or increase of more than 100 from level at remission	See table below	Not stated	

Outcome	Comparison	Result
	Prognostic factor in relation to cut-off	RR using a multivariate Cox model with time dependent covariates
ESR mm/h: Prediction of relapse risk	ESR > 15 mm/h vs. ESR < 15mm/h	RR of relapse within the next 6 weeks: 6.1 (1.9 to 18.9)

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Comments
Ref ID: 20420 D'Inca et al., 2008[129] Country: Italy	Prospective cohort	65 CD patients	Inclusion: Clinical remission (CDAI ≤ 150) for at least 3 months Demographic characteristics of CD sample: 33 male; 32 female Mean age: 43 years (18-77) Median CDAI 61 (20 to 149) 46 on 5-ASA; 11 on immunosuppressant's; 8 on no therapy 16 had prior surgery Mean time in remission 17 months ± 15	Faecal calprotectin >130 mg/kg chosen as best cut-off, with a sensitivity of 68% and specificity of 67%, a positive predictive value of 52% and negative predictive value of 79%	Faecal calprotectin < 130 mg/kg	1 year	Relapse as time to event and defined as a worsening clinical picture with CDAI >150 with an increment of more than 50 points over the baseline score.	See below	Not stated	

Outcome	Comparison of Prognostic factor in relation to cut-off	Outcome Odds ratio from multivariable analyses
ESR mm/h: Prediction of relapse risk	ESR > 25 mm/h vs. ESR < 25mm/h	OR -2.747 (0.005 to 0.847) Made assumption that OR = B coefficient, i.e. OR = eb (Exp) OR = 0.0641

1.7 Patient information and support

1.7.1 Information needs; ordered by date from oldest to most recent

Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Rees, 1983 Ref ID 6444[138] Country: UK	This study attempts to define those areas where further information is wanted by the patient and what form this should take	Cross-sectional survey	Questionnaires were sent to 73 patients with CD and they were asked to select five topics of particular interest from a list of 15.	Inclusion: Patients with CD living in Newport, Great Britain on December 31, 1981 Exclusions: None identified Baseline characteristics: Not described	None stated	Subjective data	Children
Key themes: The number of patients wanting more information about Crohn's disease in general: 64 (88%). The top five information needs of CD patients (%): Cause of CD (77%) Treatment (53%) Side effects of treatment (47%) Diet (45%) Systemic complications (44%)							

Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Mayberry, 1985 Ref ID 20455[139] Country: UK	Purpose of the study was to assess the value of a patient information booklet entitled 'Living with Crohn's Disease.	Cross-sectional survey	Questionnaire	Inclusion: Two hundred and thirty two of 350 patients with CD requested a copy of the booklet and of these, 175 (75%) completed a questionnaire about the leaflet. Ninety three nurses with CD were sent a booklet and 82 completed a questionnaire (88%). Exclusions: None identified Baseline characteristics: Not described	Glaxo Laboratories Ltd.	Self-selected response group; subjective data	Children
Key themes: Inadequate information as assessed by Welsh patients (WP) and nurses (N)with CD: Prognosis [72% WP; 68% N] Risk to family members [54% WP; 30% N] Complications of disease [47% WP; 21% N] Drug treatment [28% WP; 21% N] Surgical treatment [27% WP; 30% N] Symptoms [25% WP; 26% N] Investigations [23% WP; 15% N] Medical examination of the patient [17% WP; 11% N] Additional information requested by Welsh patients (WP) and nurses (N)with CD: Risk of cancer [75% WP; 70% N] Effect of disease on sexual activity and pregnancy [58% WP; 70% N] Effect of disease on eligibility for life insurance [58% WP; 70% N] Eligibility for disability allowances [63% WP; 60% N]							

Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Martin, 1992 Ref ID 738[140] Country: Italy	Purpose of the study was to assess patient information needs in order to correctly plan educational objectives and the choice of material for a future educational programme on IBD	Cross sectional survey	44 item self-administered questionnaire	Inclusion: 100 consecutive out-patients (50 CD and 50 UC)attending the IBD clinic of the Padua University Gastroenterology Department representing about 15% of all IBD patients under regular follow up. Exclusions: None identified Baseline characteristics: n = 50 Crohn's disease patients; mean age 38(16-78); 23 men, 27 women; 28% with secondary or higher education; mean duration of disease 7.7 years.	National Research Council and 'Associazione Roberto Farini'	Self-selected response group; subjective data	Children
Key themes: Information requested by patients with CD High priority: Causes of disease Diet Symptoms Long-term evolution (prognosis) New treatments and drugs Therapy Medium priority: Psychology							

Reference	Research Parameters	Population	Funding	Additional comments
Investigations				
Surgery				
Risks from therapy and investigations				
Cancer				
Consequences on work				

Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
O'Sullivan, 2000 Ref ID 597[141] Country: Ireland	One of four aims of this study was to identify educational needs in IBS	An open-ended survey question: 'What are the main question(s) you have about your bowel disorder?'	Patients were instructed to give a written response to the study enquiry. Responses were labelled according to their central theme, grouped into categories and ranked in priority order.	Inclusion: Patients with IBD and IBS (60 with CD) were recruited through gastroenterology outpatient clinics Exclusions: None identified Baseline characteristics: 68% female; mean age 38 ± 19; median disease duration in years 5.35 (0-29).	None stated	Self-selected response group; subjective data	Children
Key themes: The top five information needs of CD patients (%): Prognosis (17) Cancer (17) Medications (10) Surgery (10) Miscellaneous (10)							

Reference	Research Parameters			Population	Funding	Additional comments	
	Research question	Theoretical approach	Data collection	Population and sample collection	Source of funding	Limitations	Evidence gap
Casellas, 2004 Ref ID 435[142] Country: Spain	Purpose of the study was to investigate patient opinion re the quality and adequacy of the medical resources they use.	Cross-sectional opinion poll using an anonymous self-report survey	Postal survey	Inclusion: Patients diagnosed with ulcerative colitis or Crohn's disease who had enrolled in Unitat d'Atencio Crohn-Colitis Exclusions: None identified Baseline characteristics: n = 115 Crohn's disease patients; median age 32 (24-42); 52 men, 63 women; 61% with secondary or higher education; 55% employed, 13% retired, 14% student, 18% other.	Not stated	Self selected response group; subjective data	Children
Key themes: Areas in which patients lacked information: Causes of disease (65 patients) Potential outcome of disease (60 patients) Complications that may arise (58 patients) Possibility of transmission to offspring or contagion (36 patients) Management of disease (24 patients) Need for surgical procedure (19 patients)							

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