National Clinical Guideline Centre

Ulcerative colitis

Appendices H-N

Forest plots, ROC curves, NMAs, unit costs, CEAs, research recommendations and author definitions

Ulcerative colitis

Clinical guideline

June 2013

NICE's original guidance on Ulcerative colitis: management in adults, children and young people was published in June 2013 and has undergone an 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 2013 replaced by the 2019 update.

Final version

Commissioned by the National Institute for Health and Care Excellence

Funding
National Institute for Health and Care Excellence

Contents

1 Appendix H: Forest plots and ROC curves

1.1 Induction of remission for a mild to moderate inflammatory exacerbation of ulcerative colitis

1.1.1

1.1.1.1

Please note that evidence on treatments for inducing remission in people with mild-to-moderate ulcerative colitis was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

Figure 1: Clinical remission

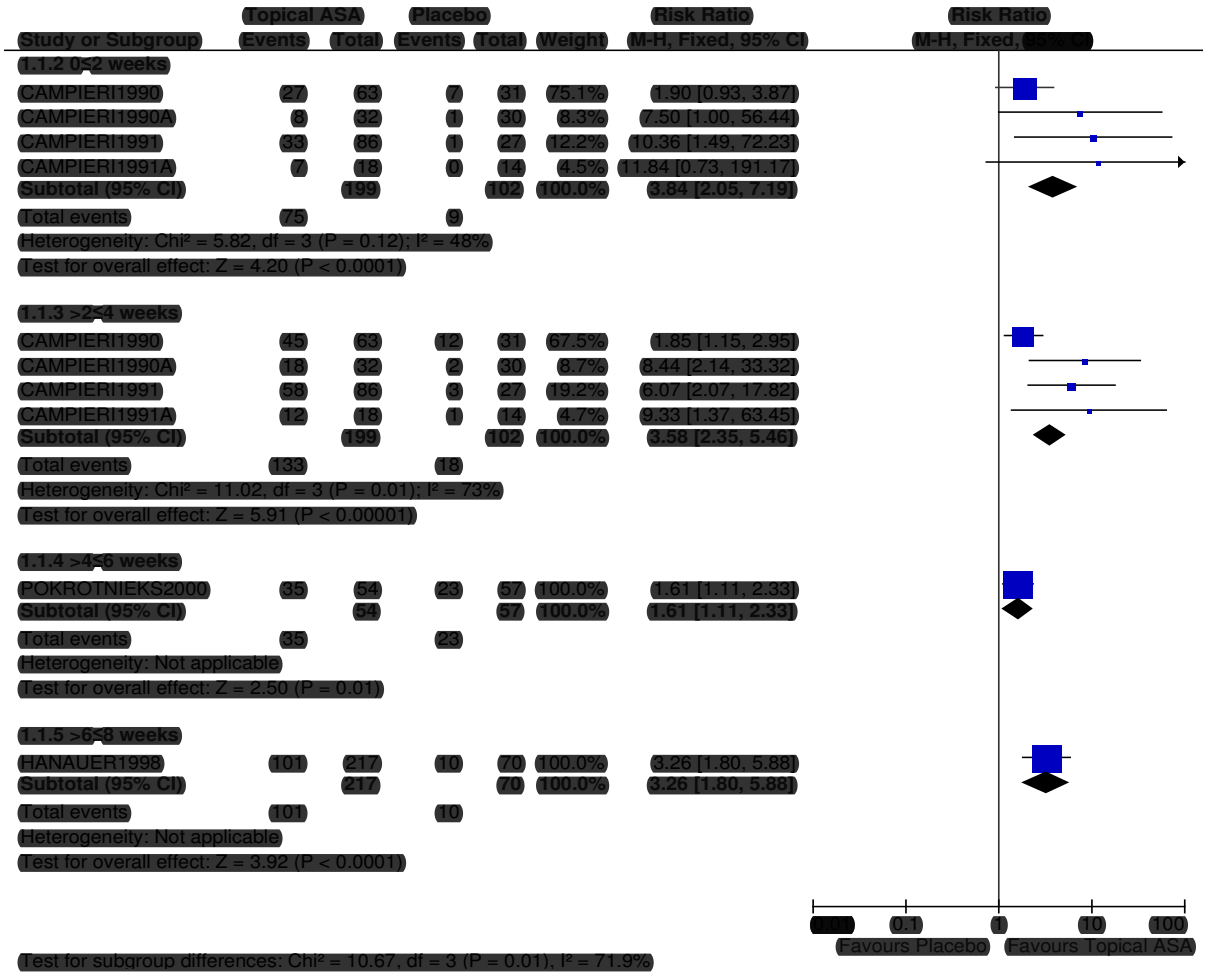


Figure 2: Clinical remission >2≤4 weeks by extent of disease

Figure 3: Clinical remission >2≤4 weeks, random effects

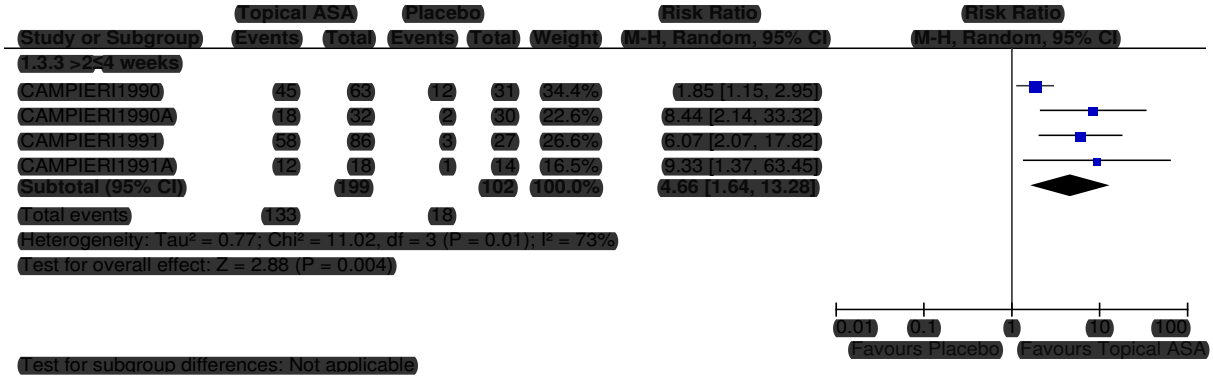


Figure 4: Clinical improvement

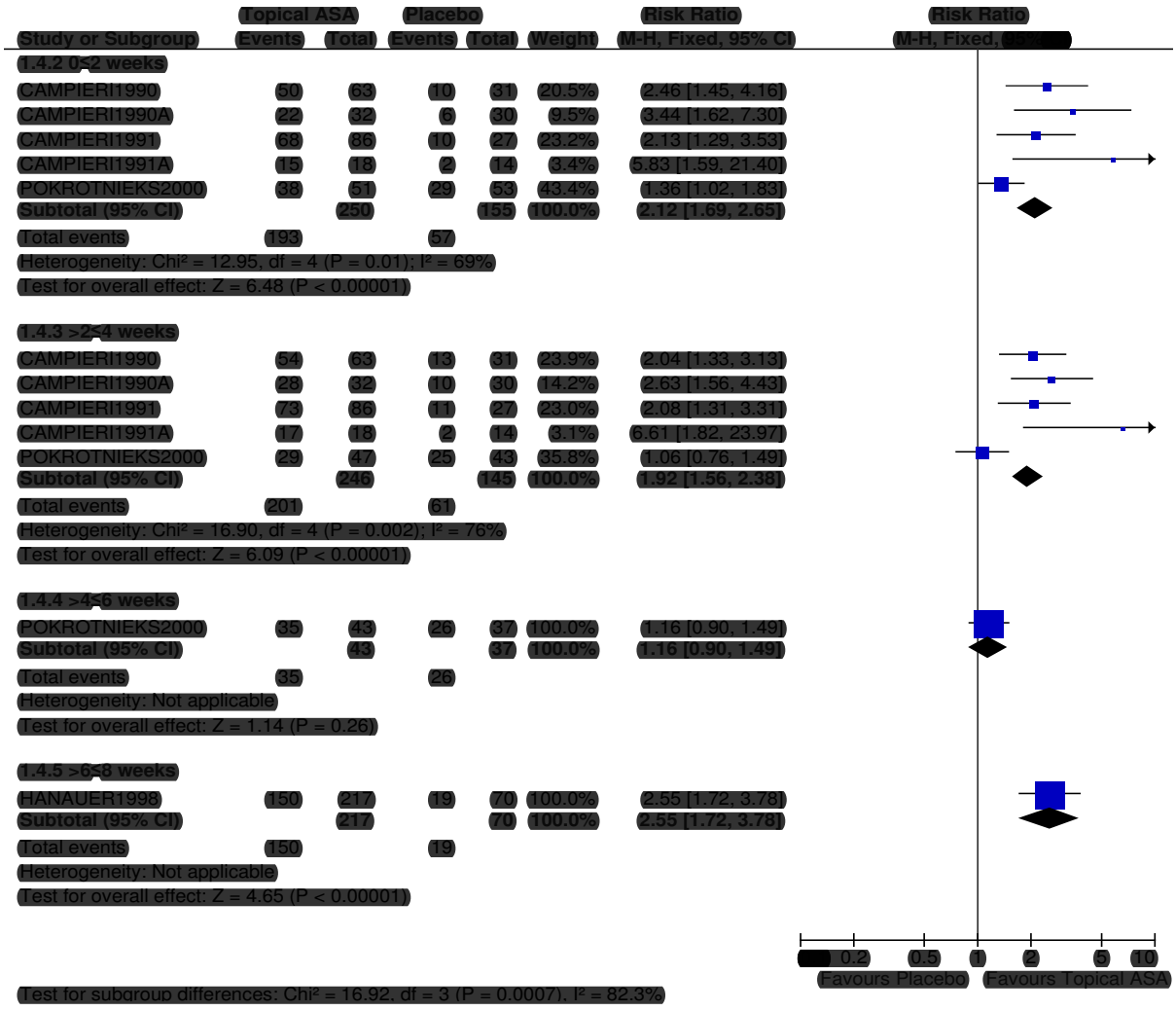


Figure 5: Clinical improvement 0≤2 weeks by extent of disease

Figure 6: Clinical improvement >2≤4 weeks by extent of disease

Figure 7: Clinical improvement 0≤2 weeks and >2≤4 weeks , random effects

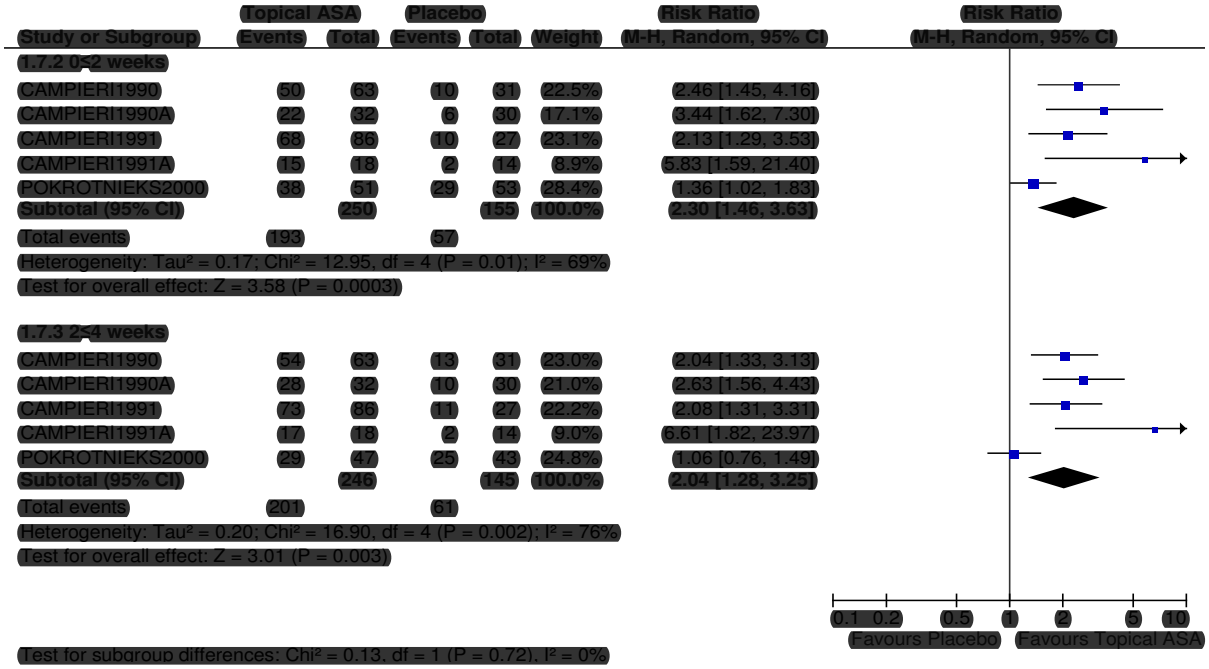


Figure 8: Endoscopic remission

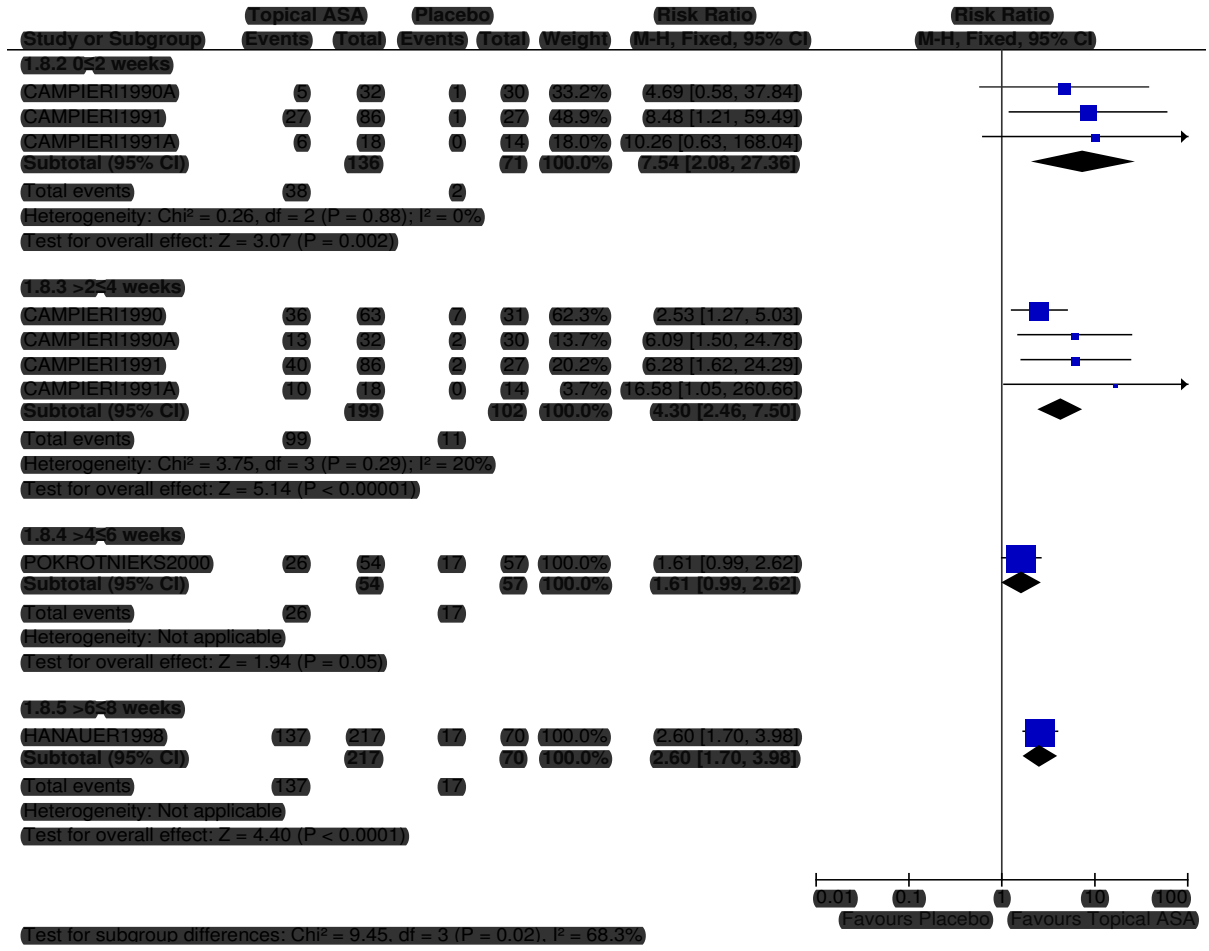


Figure 9: Clinical and endoscopic remission

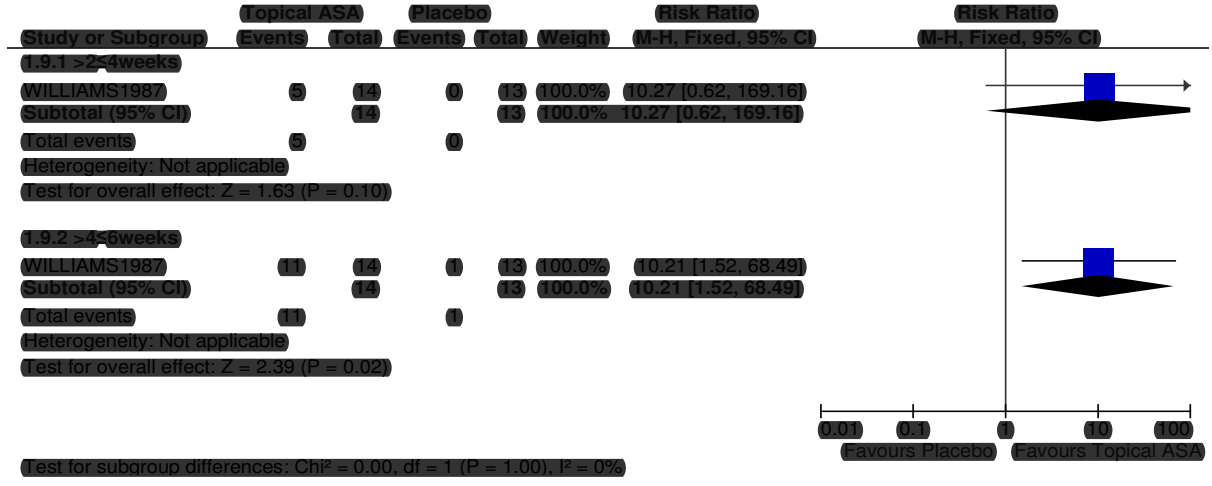


Figure 10: Adverse events

Figure 11: Serious adverse events

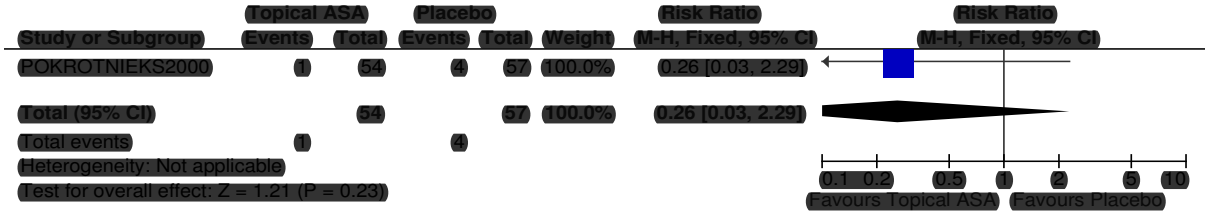
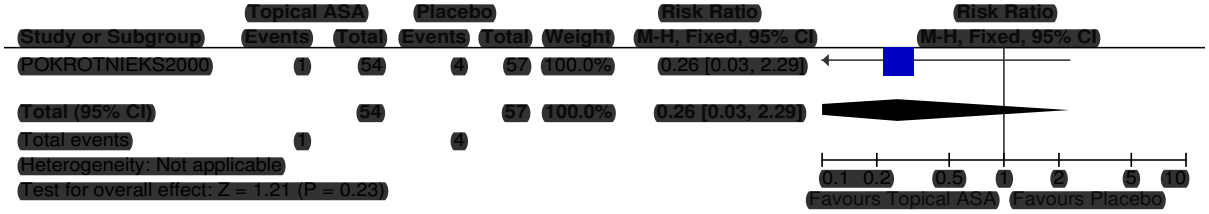


Figure 12: Hospitalisations



1.1.1.2 Preparation comparisons - Foam enema versus liquid enema

Figure 13: Clinical remission

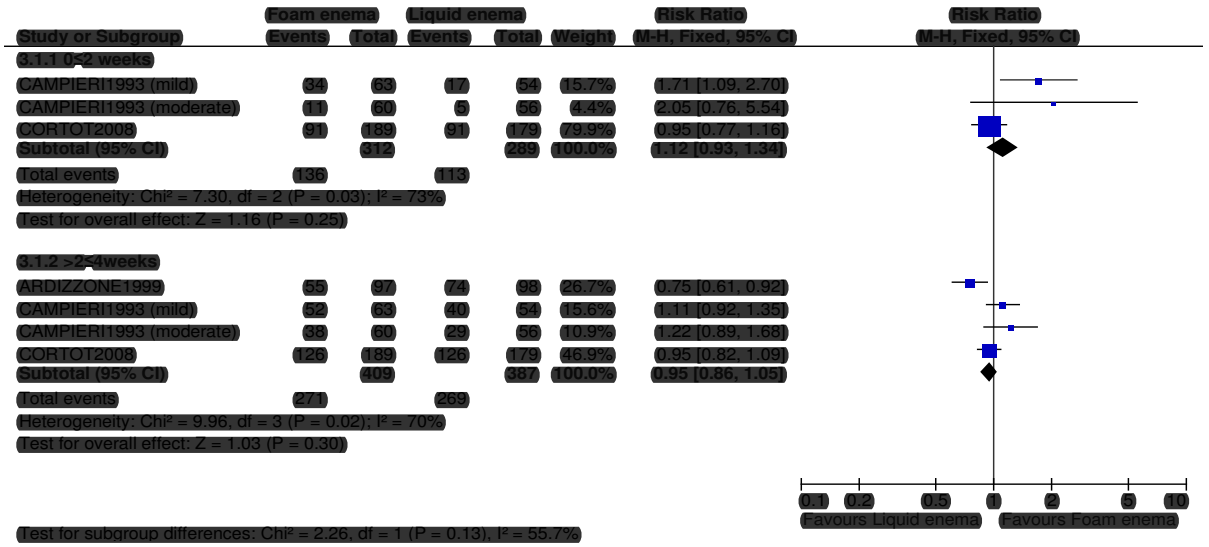


Figure 14: Clinical remission 0≤2 weeks and >2≤4 weeks, random effects

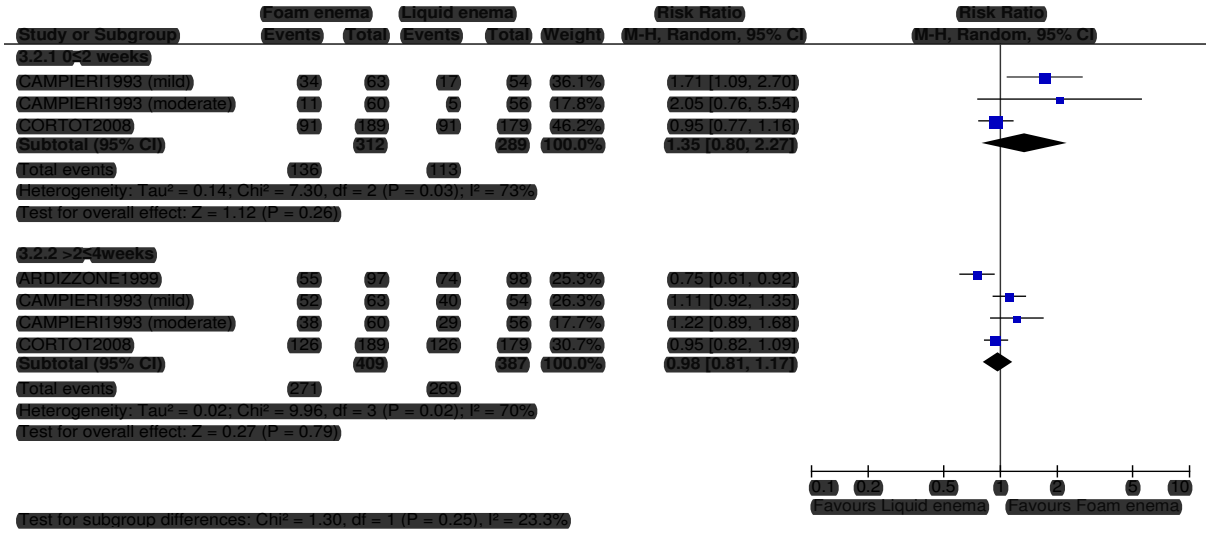


Figure 15: Clinical improvement

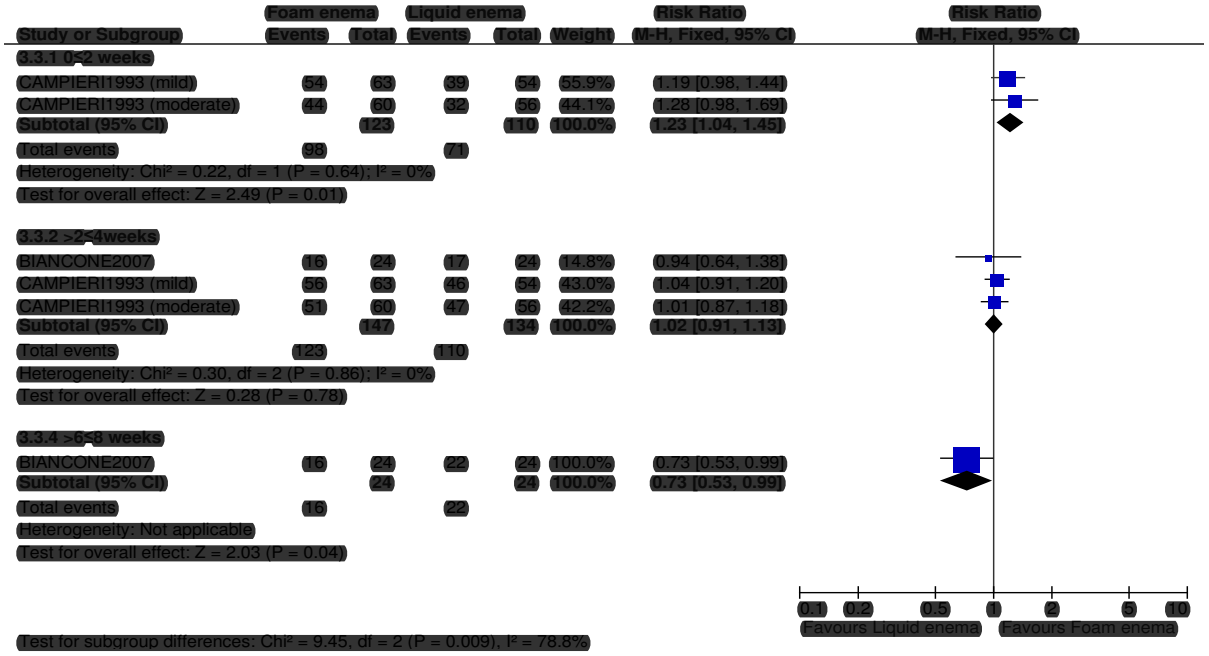


Figure 16: Endoscopic remission

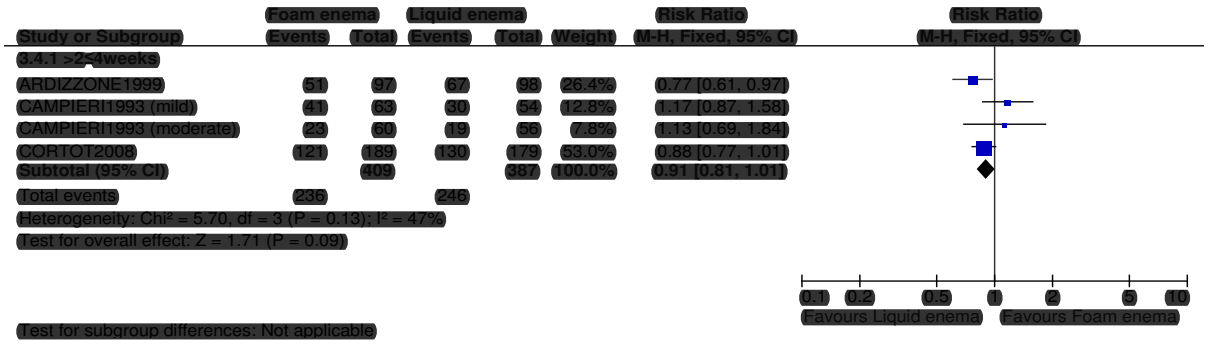


Figure 17: Clinical and endoscopic remission

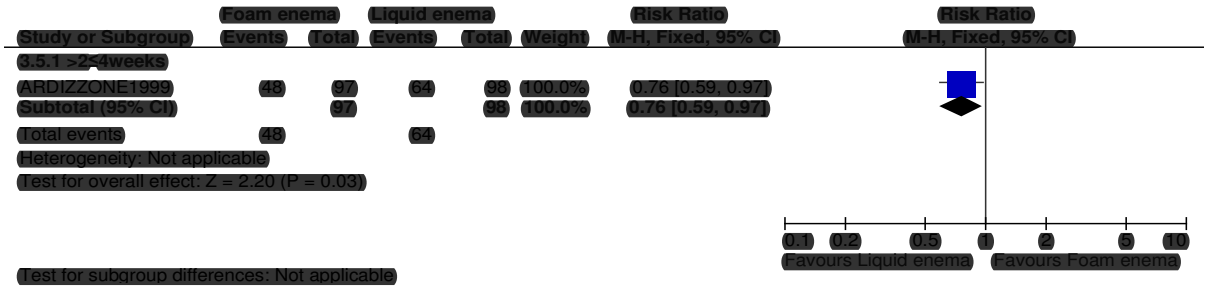


Figure 18: Adverse events

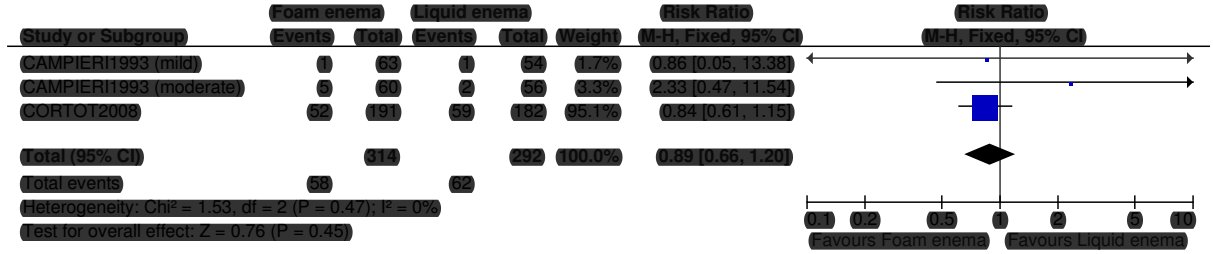
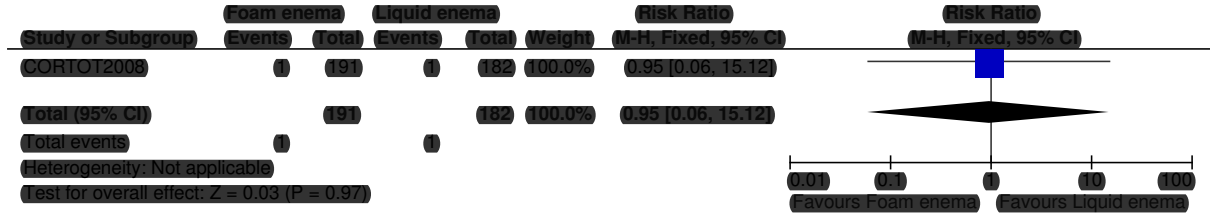


Figure 19: Serious adverse events



1.1.1.3 Preparation comparisons – Suppository versus liquid enema

Figure 20: Clinical remission

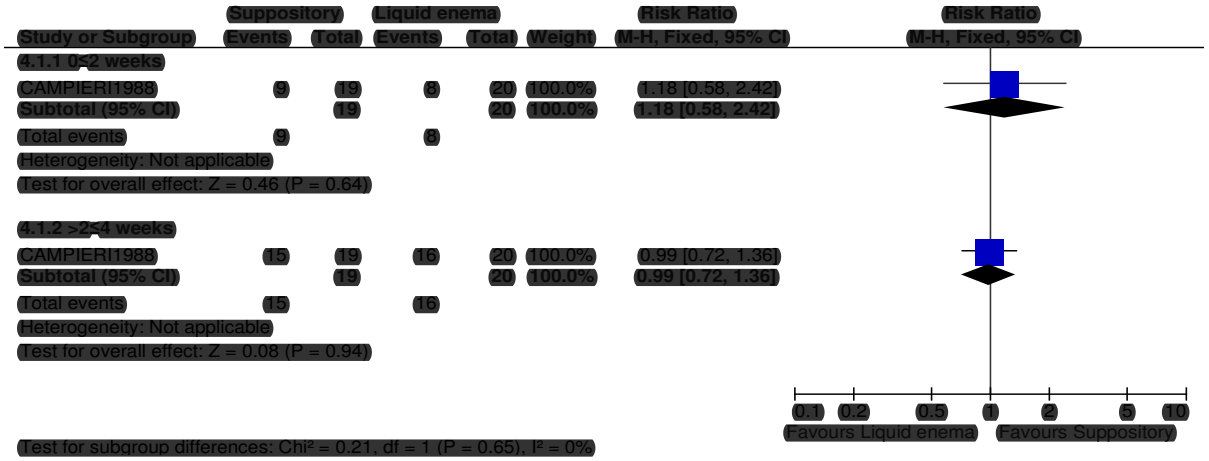


Figure 21: Clinical Improvement

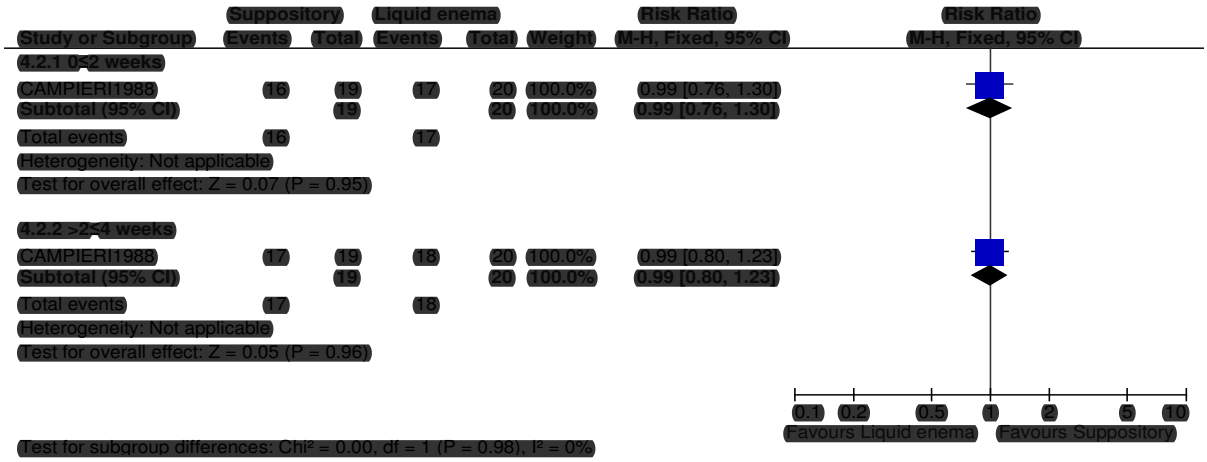
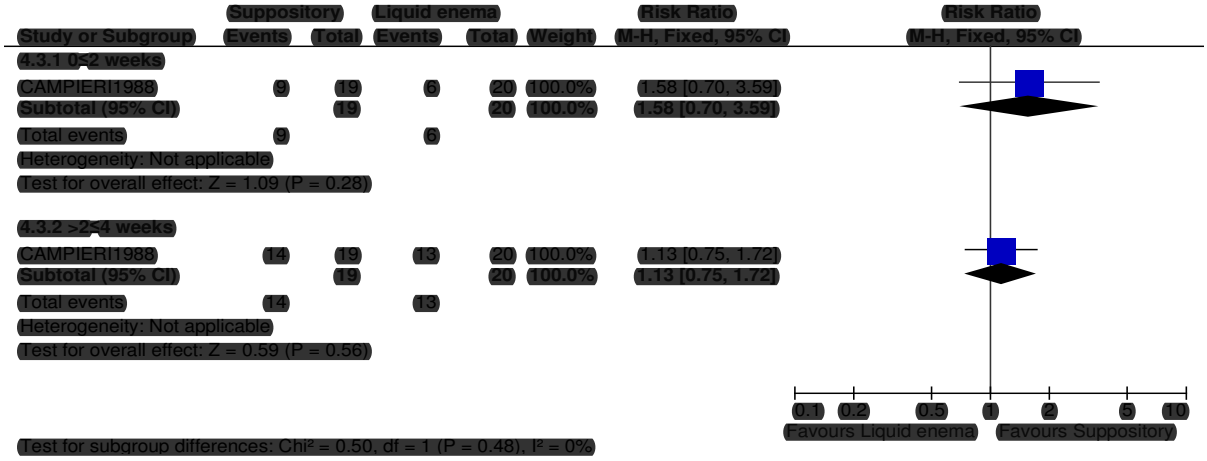


Figure 22: Endoscopic remission



1.1.1.4 Dose comparisons

Figure 23: Clinical remission – 1g versus 1.5g

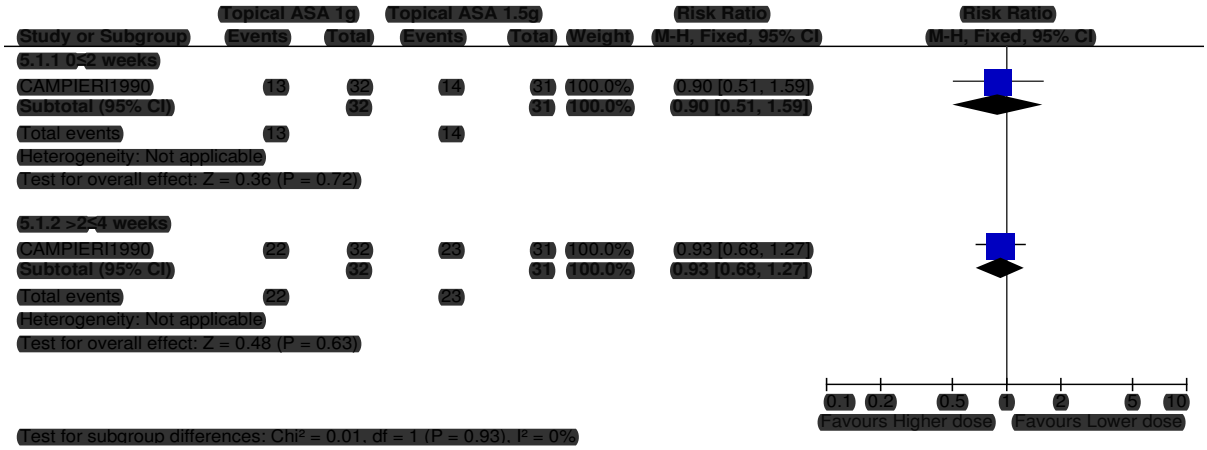


Figure 24: Clinical remission – 1g versus 2g

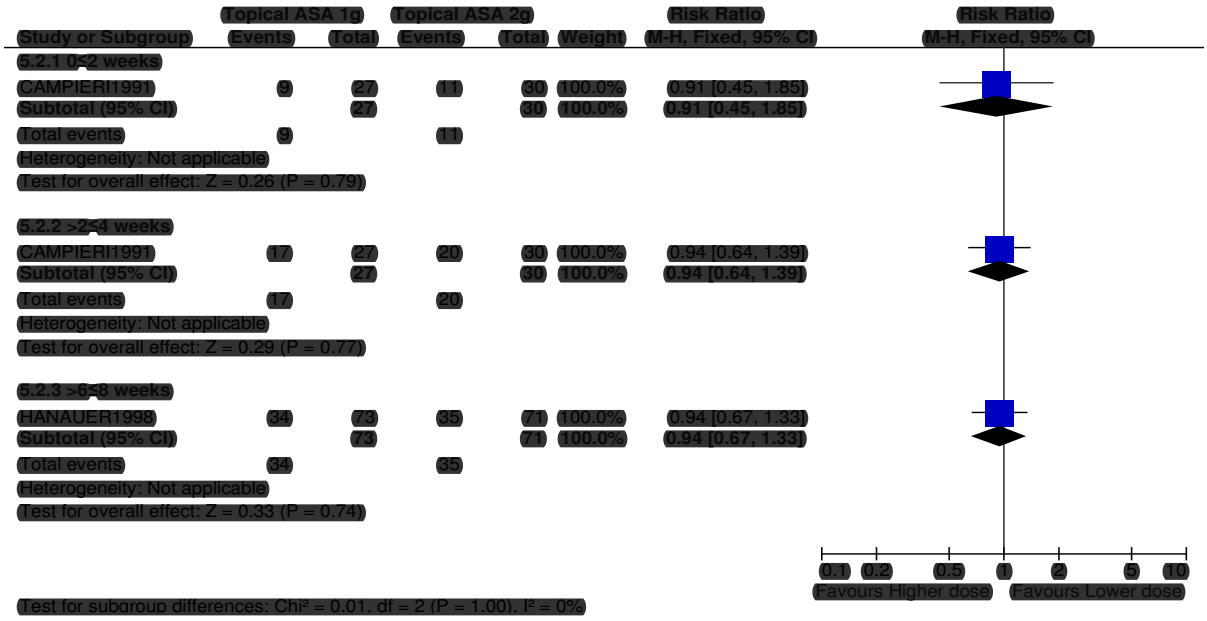


Figure 25: Clinical remission – 1g versus 4g

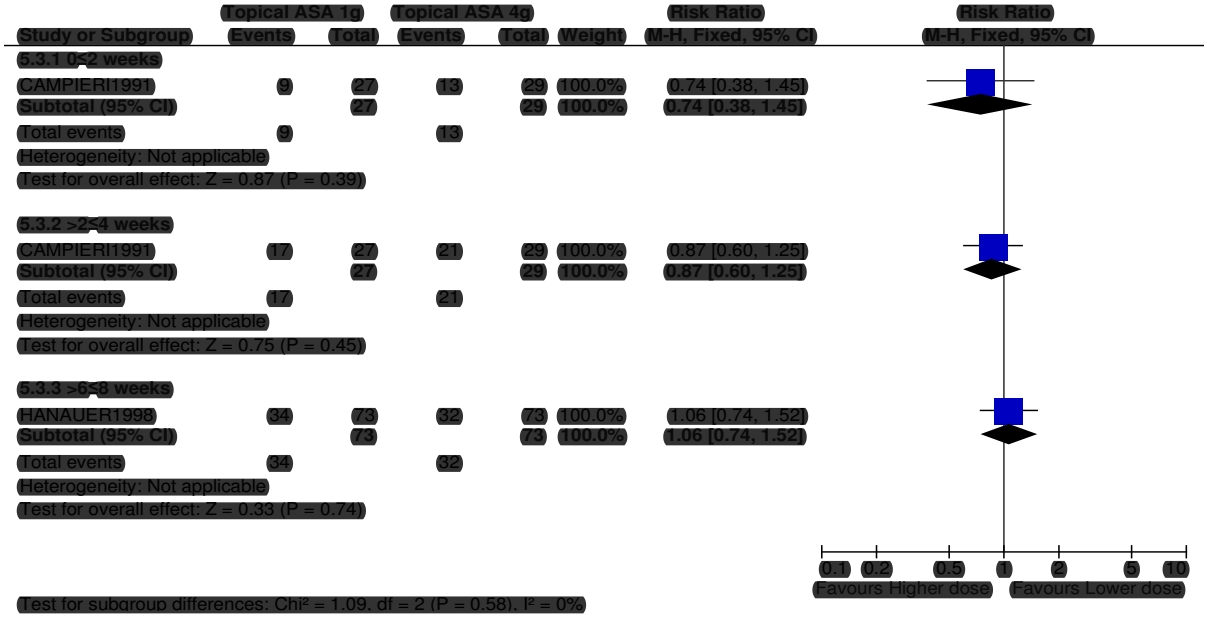


Figure 26: Clinical remission – 2g versus 4g

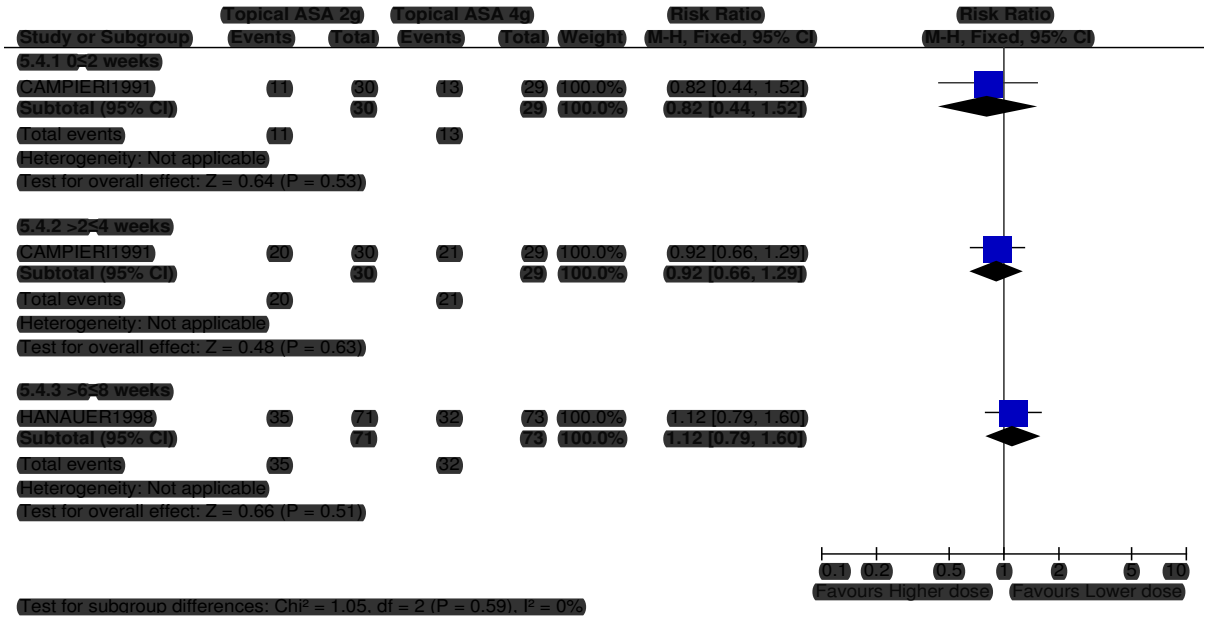


Figure 27: Clinical improvement – 1g versus 1.5g

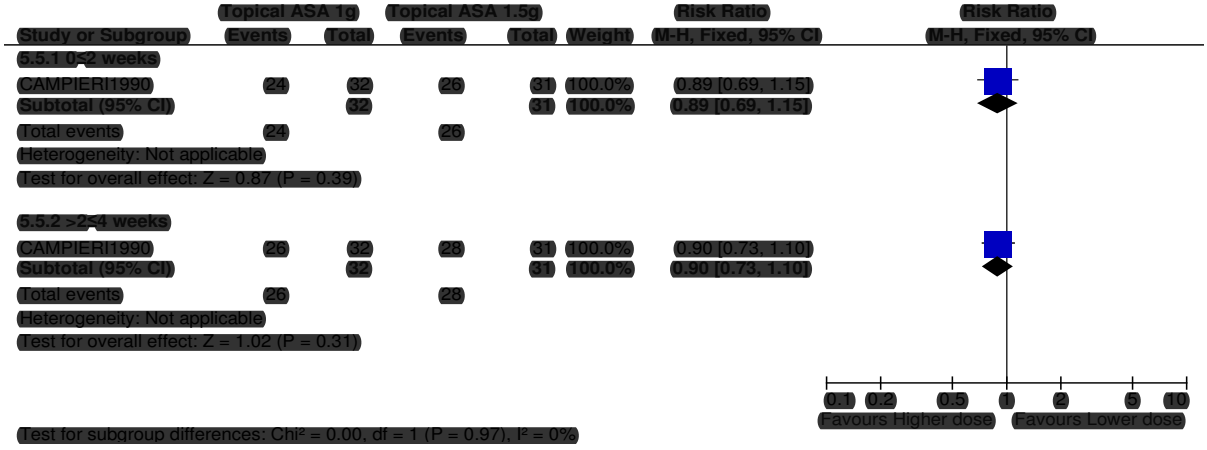


Figure 28: Clinical improvement – 1g versus 2g

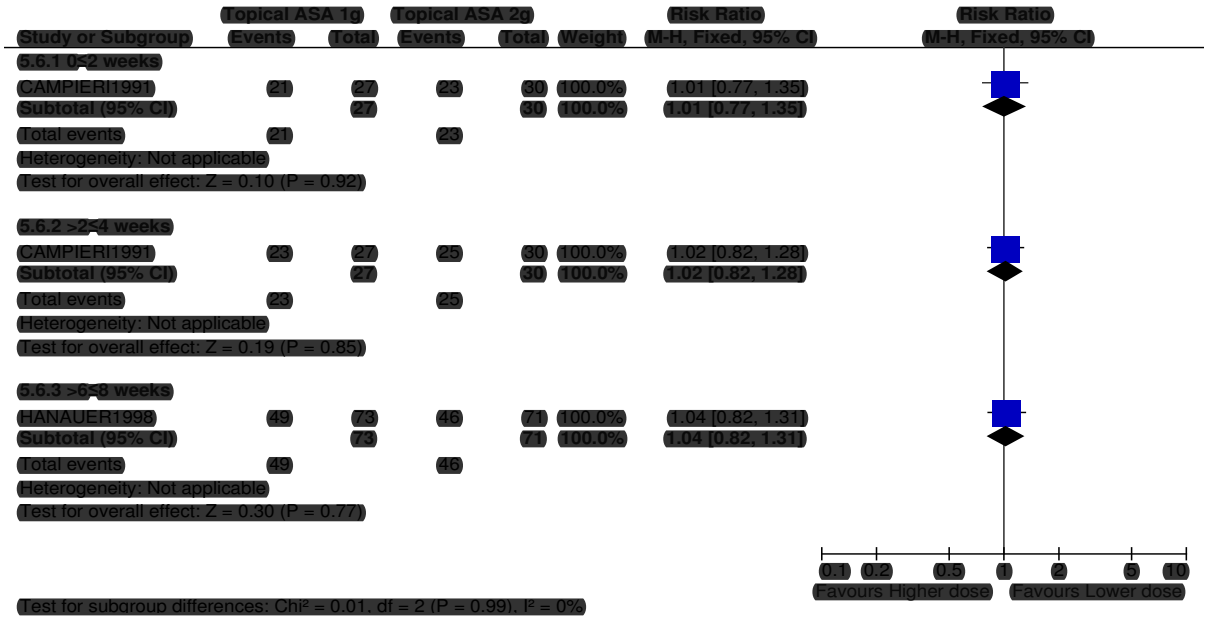


Figure 29: Clinical improvement – 1g versus 4g

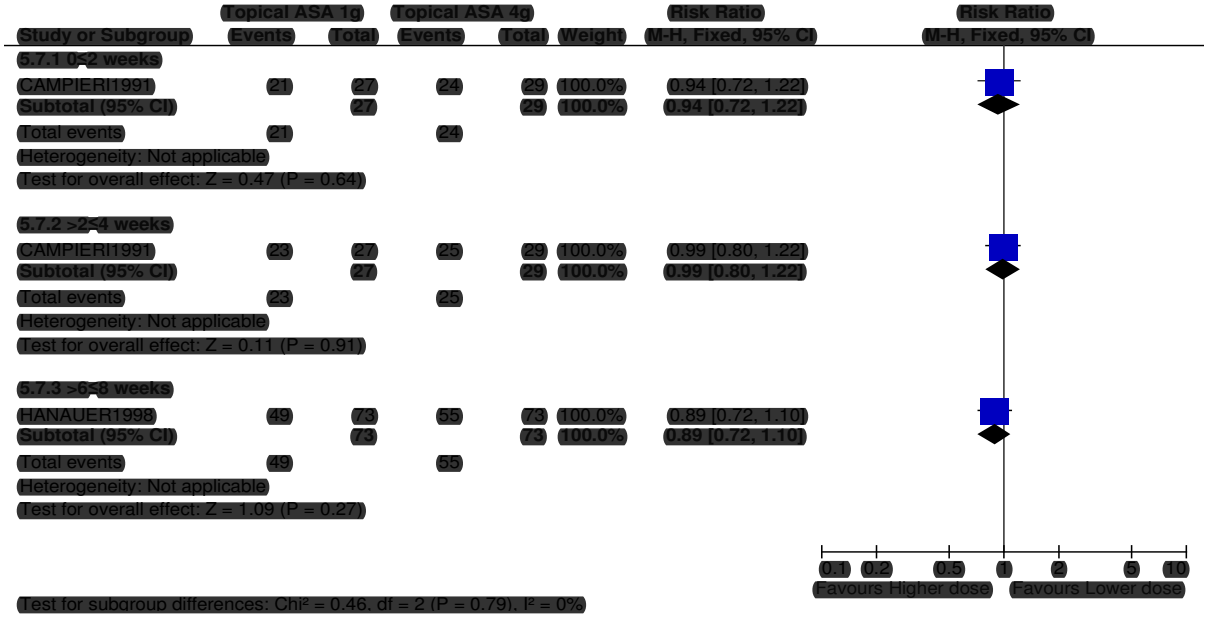


Figure 30: Clinical improvement – 2g versus 4g

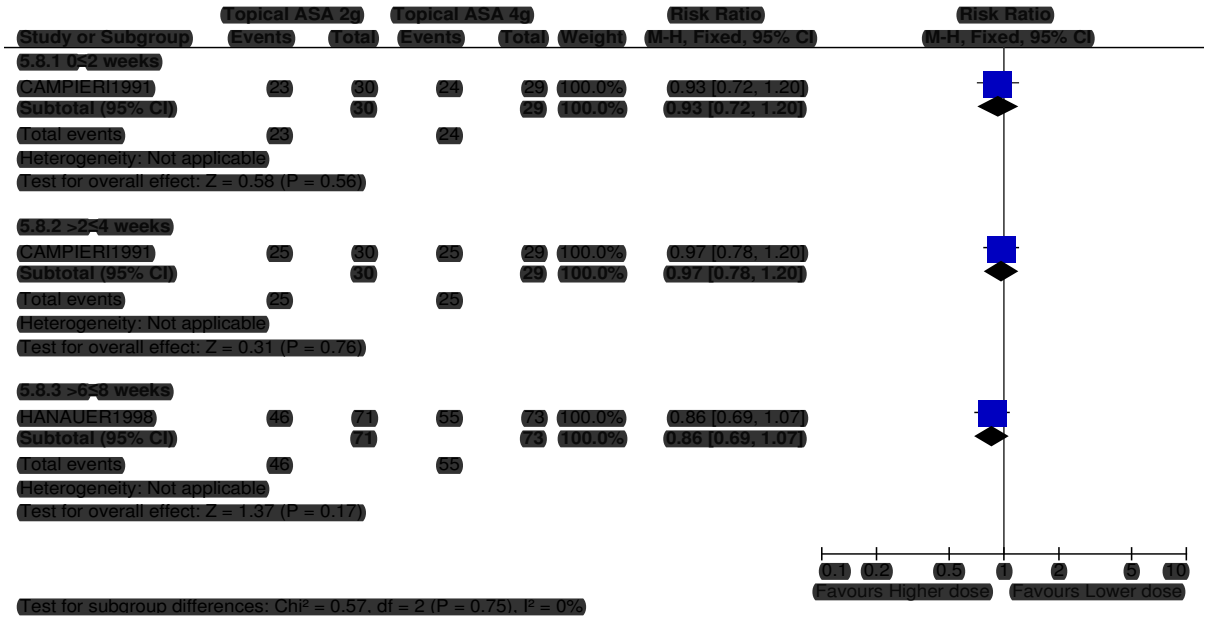


Figure 31: Endoscopic remission – 1g versus 1.5g

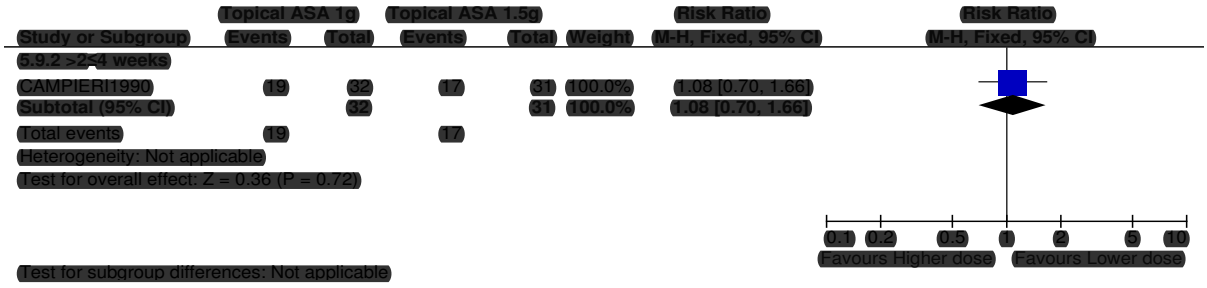


Figure 32: Endoscopic remission – 1g versus 2g

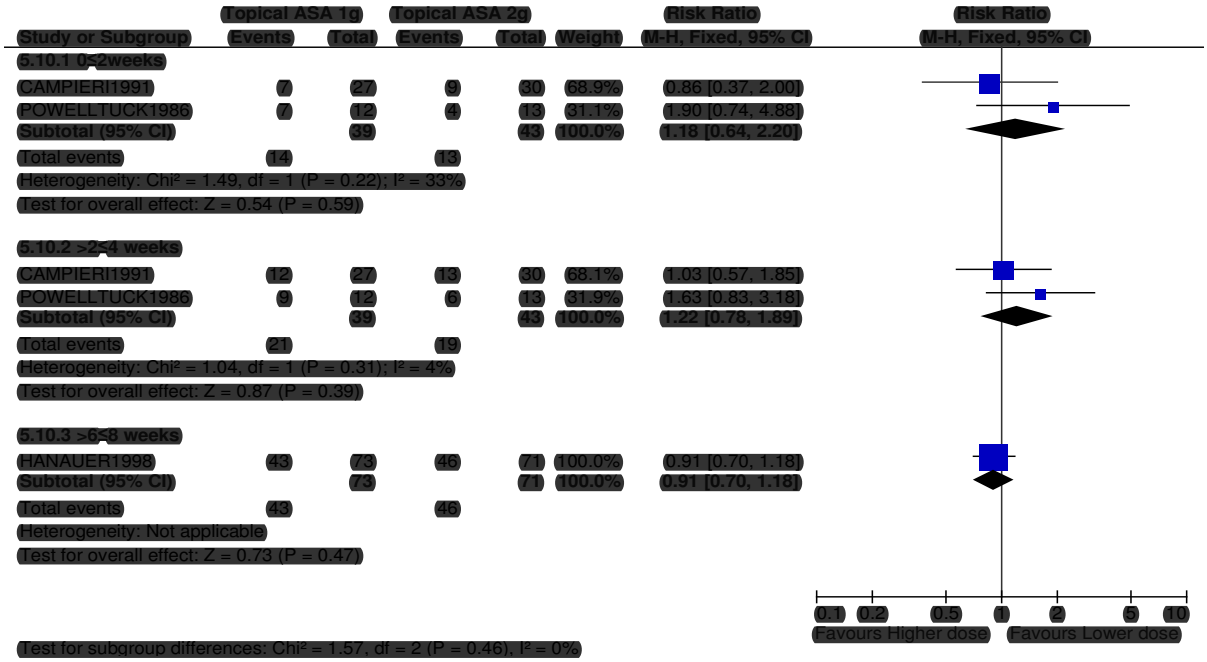


Figure 33: Endoscopic remission – 1g versus 4g

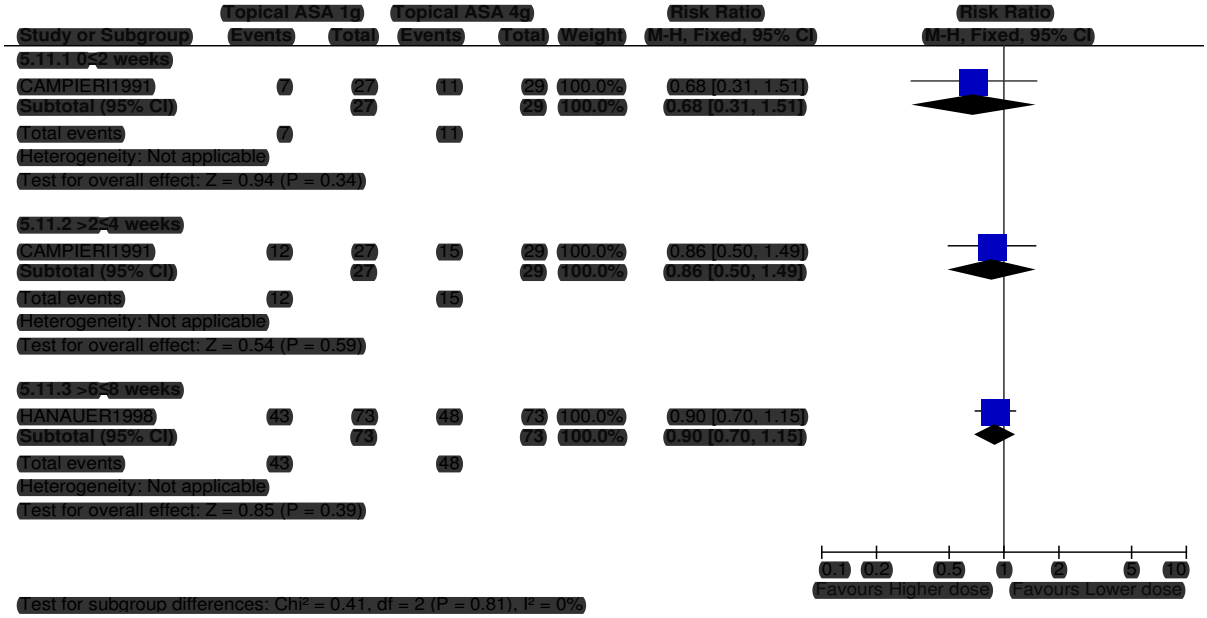


Figure 34: Endoscopic remission – 2g versus 4g

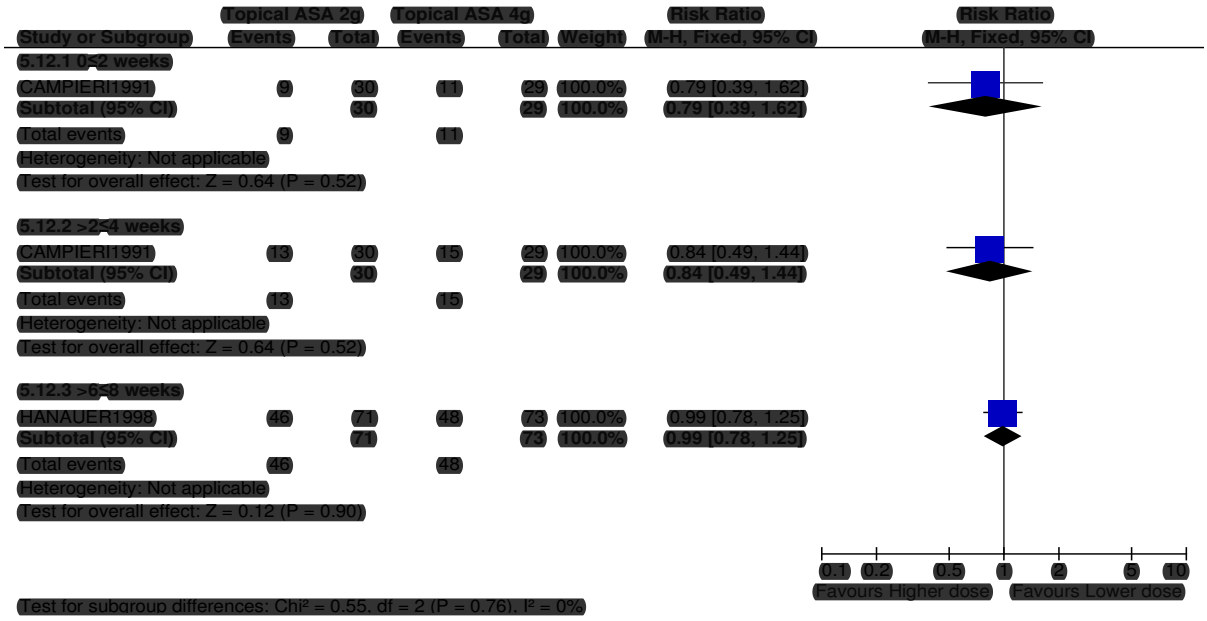


Figure 35: Clinical and endoscopic remission – 1g versus 2g

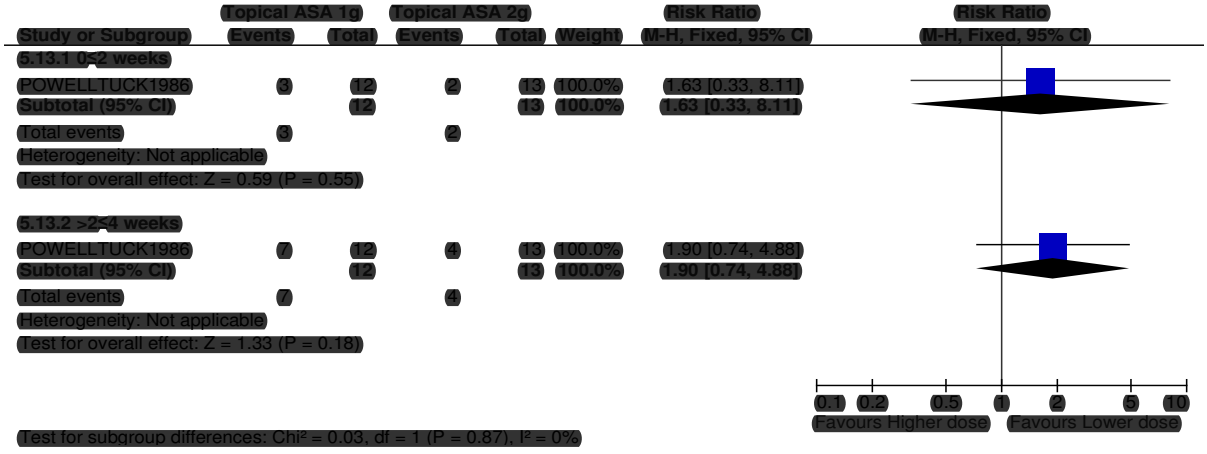
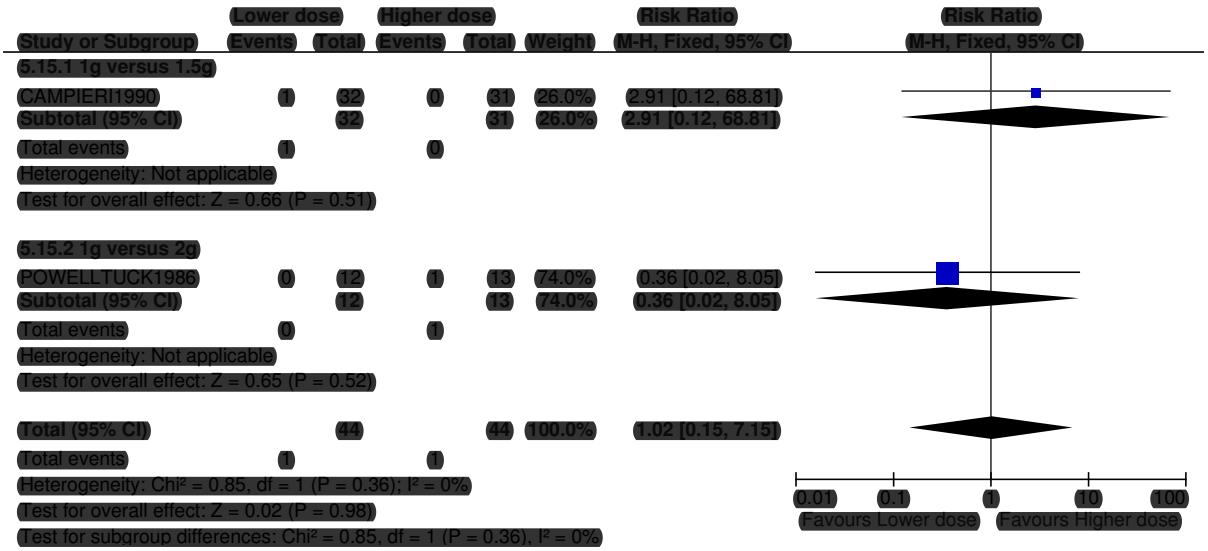


Figure 36: Adverse events



1.1.1.5 Regimen comparison – once versus twice a day

Figure 37: Clinical remission

Figure 38: Adverse events

1.1.1.6 Regimen and dose comparison – once a day (1g) versus three times a day (1.5g)

Figure 39: Clinical remission

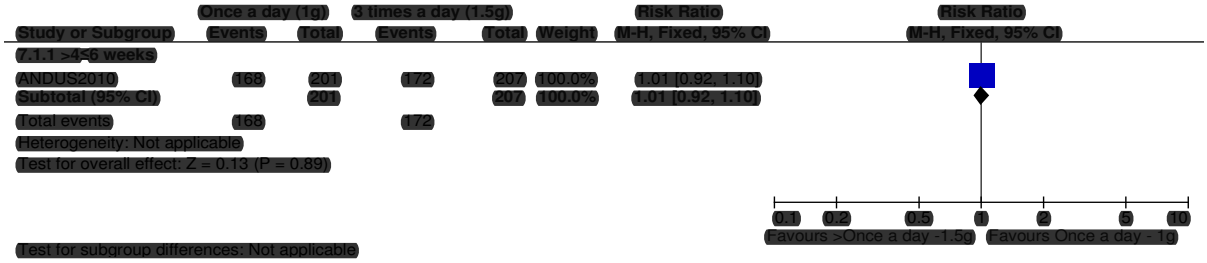


Figure 40: Clinical improvement

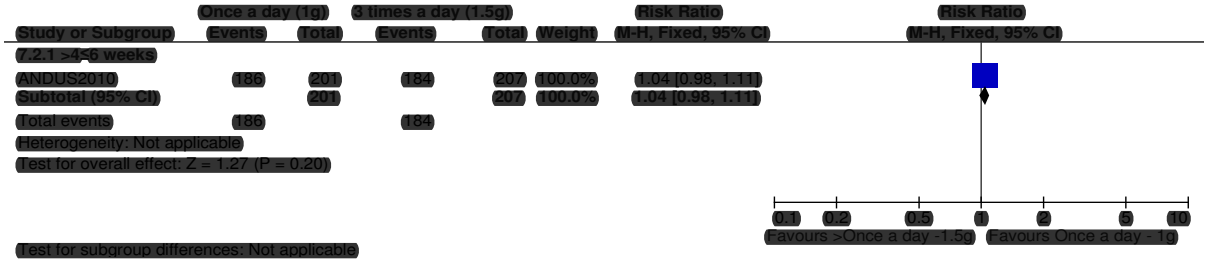


Figure 41: Endoscopic remission

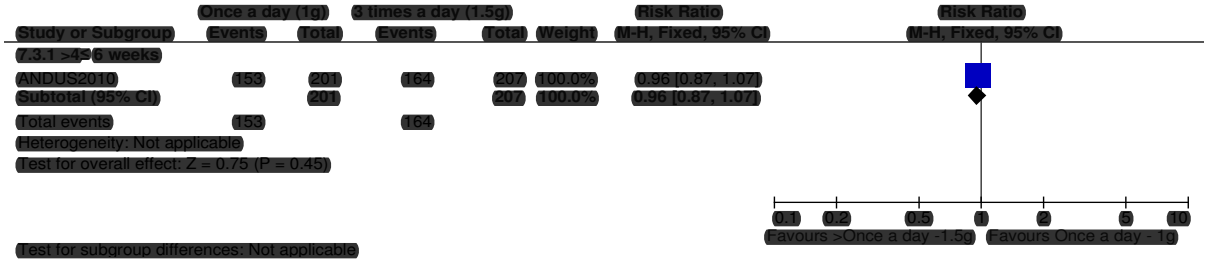


Figure 42: Adverse events

Figure 43: Serious adverse events

Figure 44: Hospitalisations

1.1.2 Topical corticosteroids

Figure 45: Endoscopic remission (>4≤6weeks)

Figure 46: Clinical and endoscopic remission (>4≤6weeks)

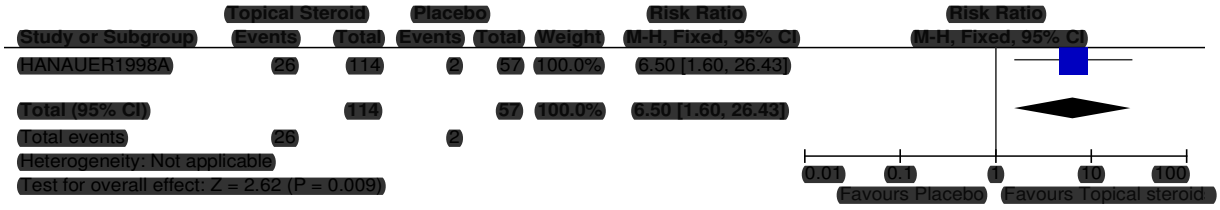
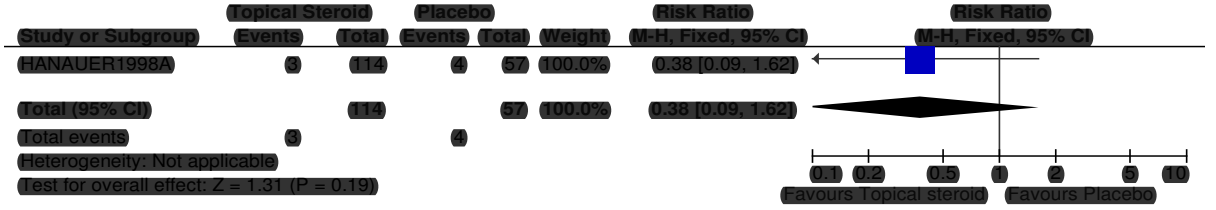


Figure 47: Serious adverse events



1.1.2.1 Preparation comparison - Foam versus liquid enema

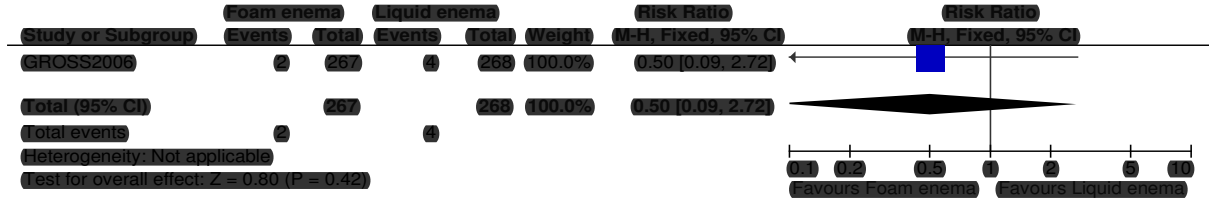
Figure 48: Clinical remission (>2≤4weeks)

Figure 49: Clinical improvement (>2≤4weeks)

Figure 50: Endoscopic remission (>2≤4weeks)

Figure 51: Adverse events

Figure 52: Serious adverse events



1.1.2.2 Dose comparison – Budesonide

Figure 53: Endoscopic remission (>4≤6weeks)

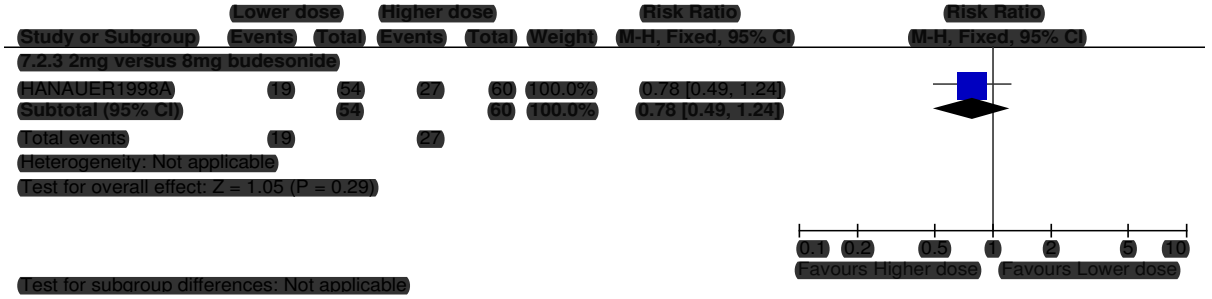


Figure 54: Clinical and endoscopic remission

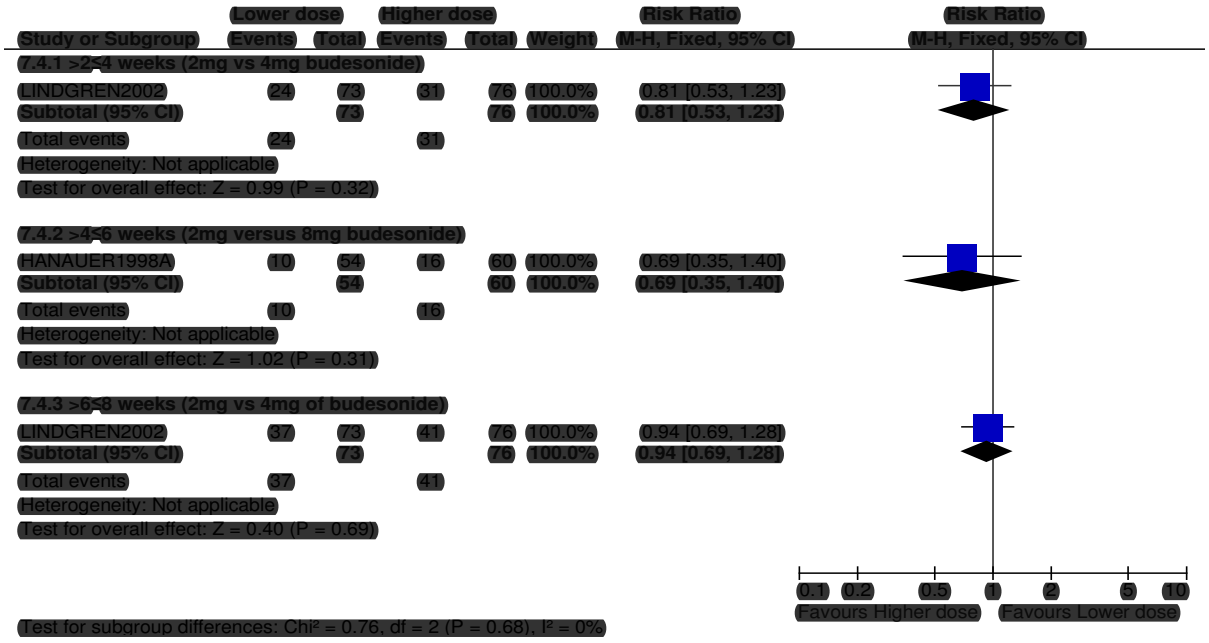


Figure 55: Adverse events

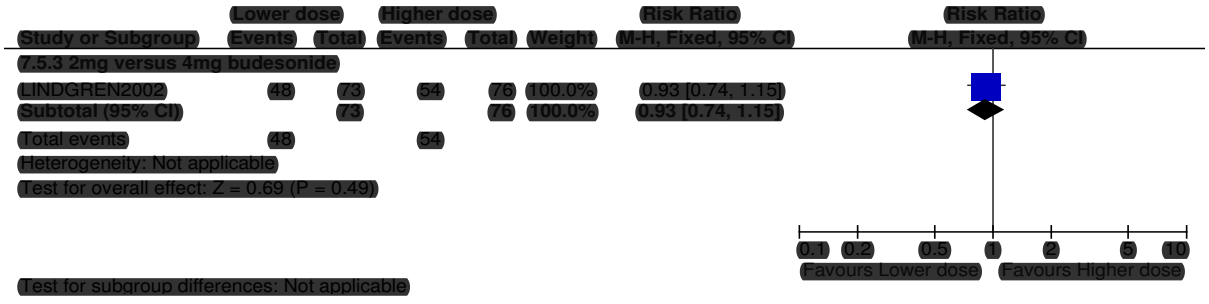
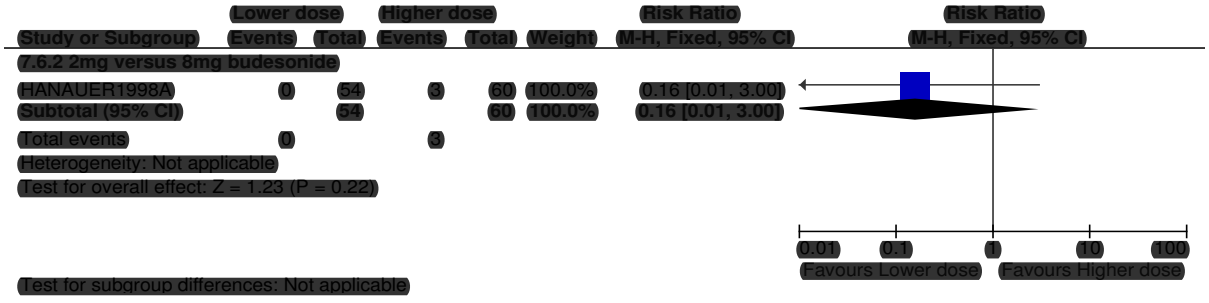


Figure 56: Serious adverse events



1.1.3 Interclass comparison

1.1.3.1 Budesonide foam enema versus hydrocortisone foam enema

Figure 57: Clinical remission (>6≤8 weeks)

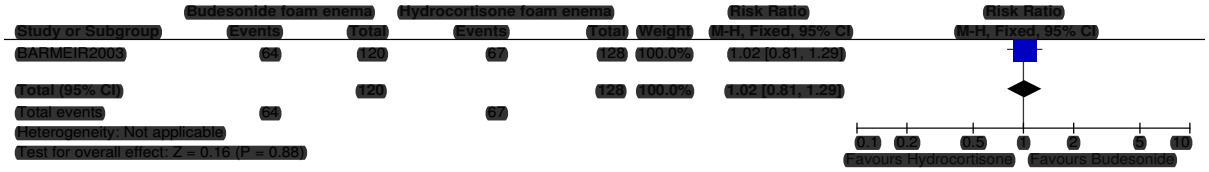


Figure 58: Adverse events

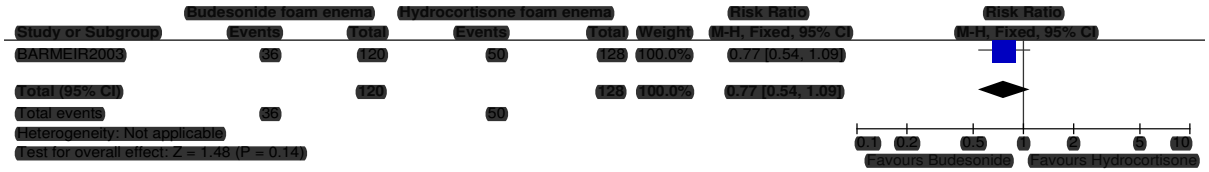
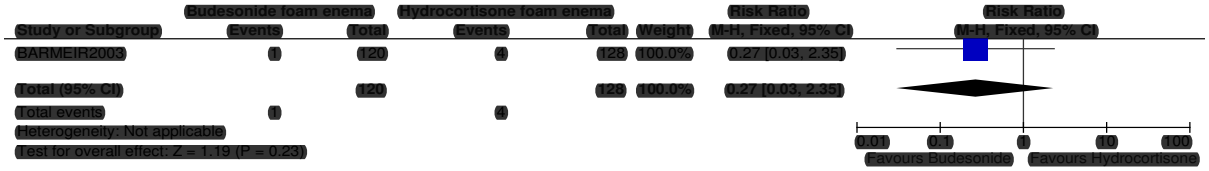


Figure 59: Serious adverse events



1.1.3.2 Budesonide liquid enema versus prednisolone liquid enema

Figure 60: Endoscopic remission – Fixed effects

Figure 61: Endoscopic remission – random effects

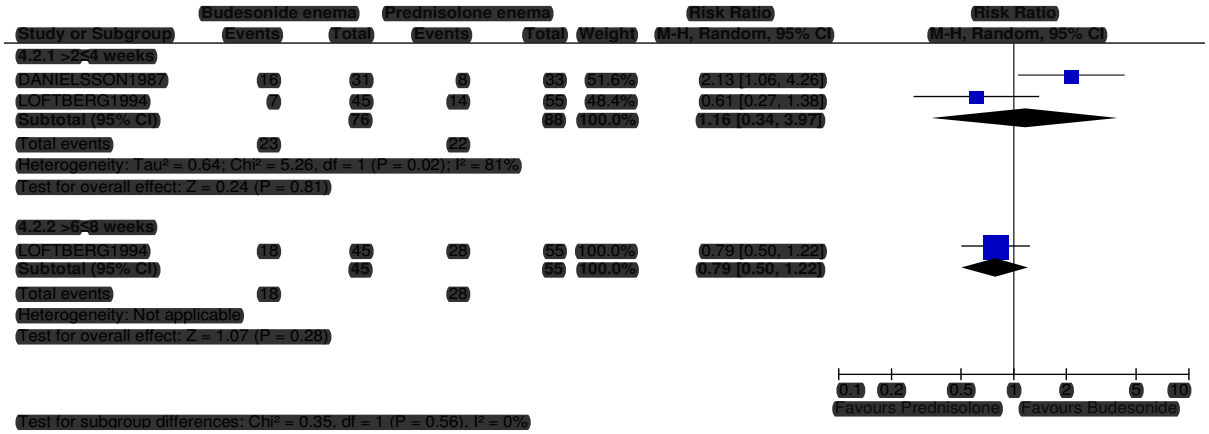
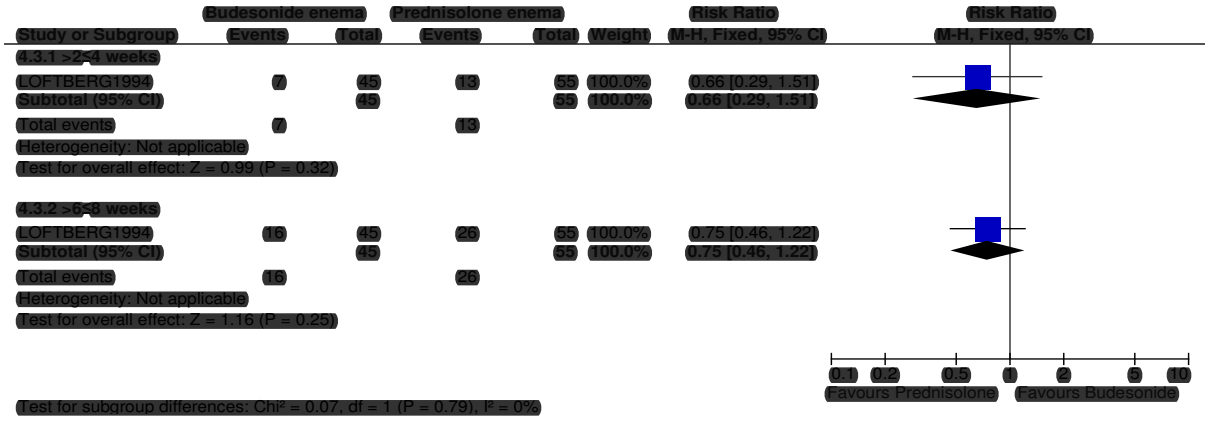
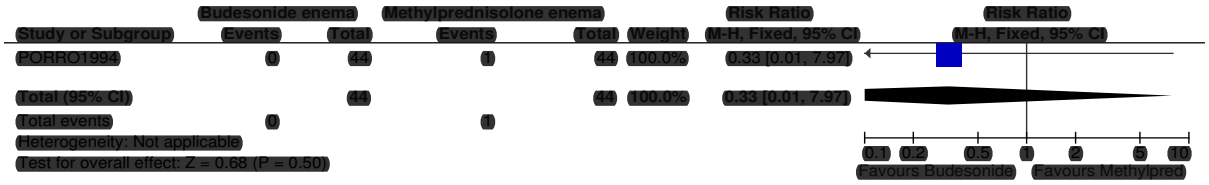


Figure 62: Clinical and endoscopic remission



1.1.3.3 Budesonide liquid enema versus methylprednisolone liquid enema

Figure 63: Hospitalisations



Note: *Methylprednisolone is the type of prednisolone used in this study*

1.1.4 Interclass and preparation comparison

1.1.4.1 Budesonide liquid enema versus hydrocortisone foam enema

Figure 64: Endoscopic remission (>2≤4weeks)

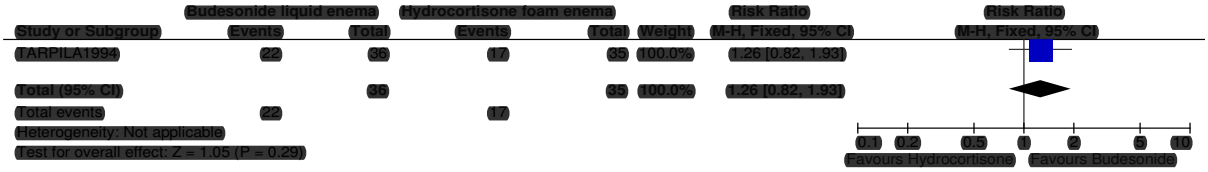
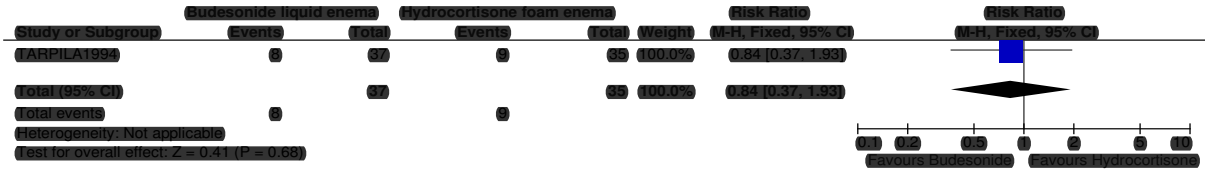


Figure 65: Adverse events



1.1.5 Topical aminosalicylates versus topical corticosteroids

Figure 66: Clinical remission

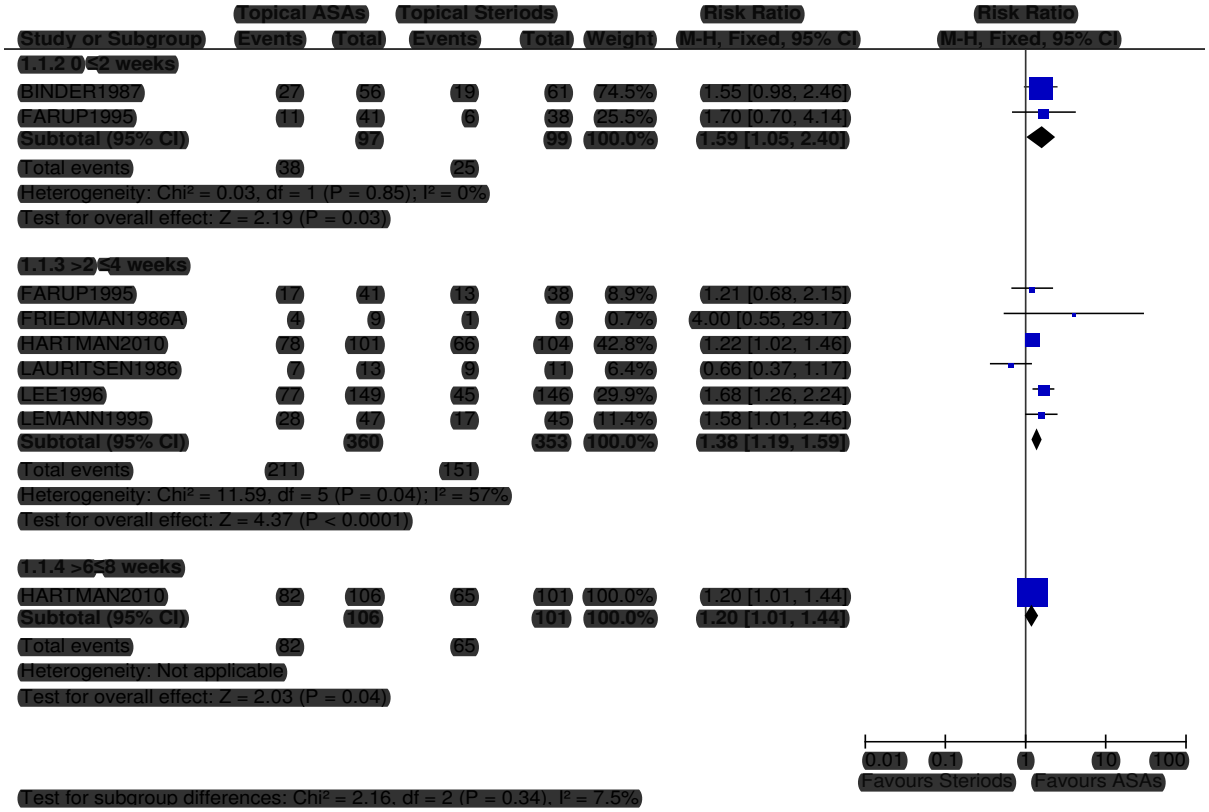


Figure 67: Clinical remission >2≤4 weeks, random effects

Figure 68: Clinical improvement

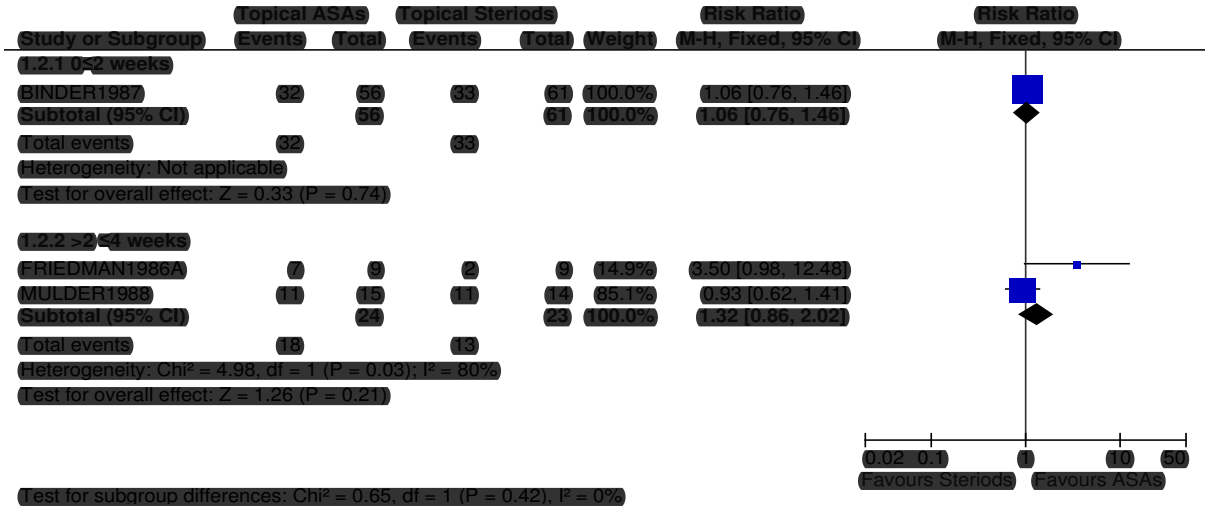


Figure 69: Clinical improvement >2≤4 weeks, random effects

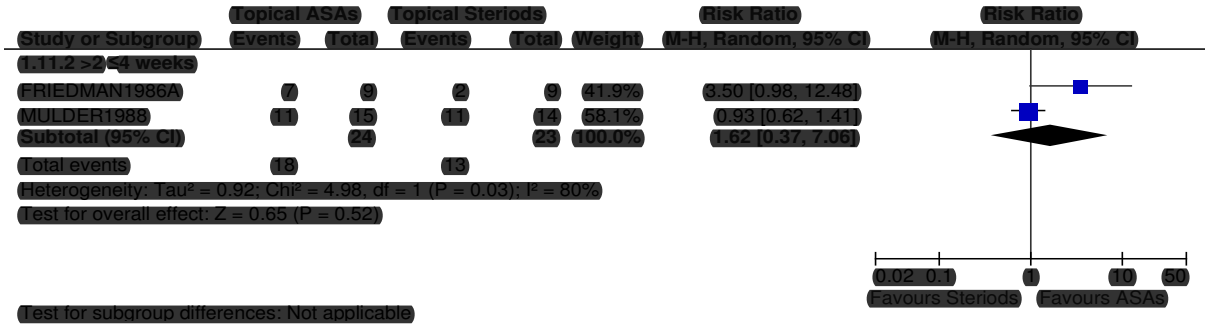


Figure 70: Quality of life

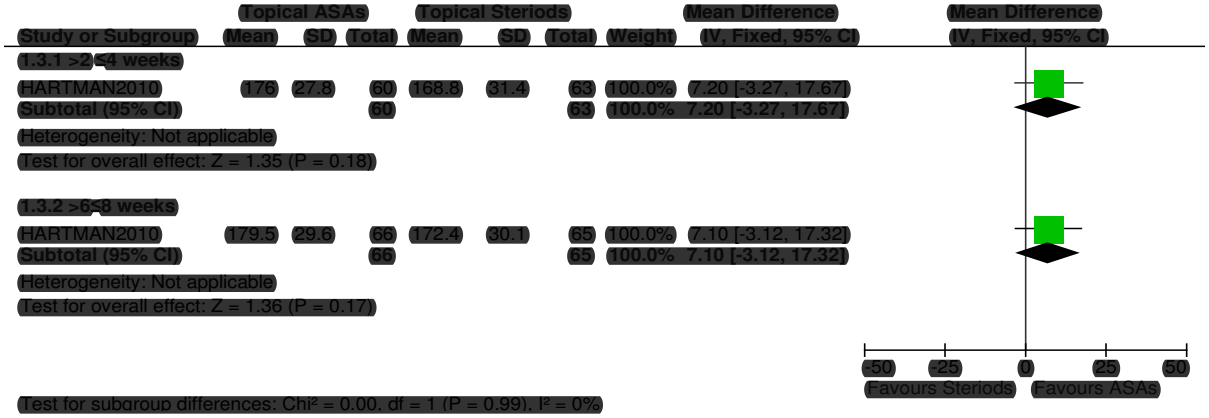


Figure 71: Endoscopic remission

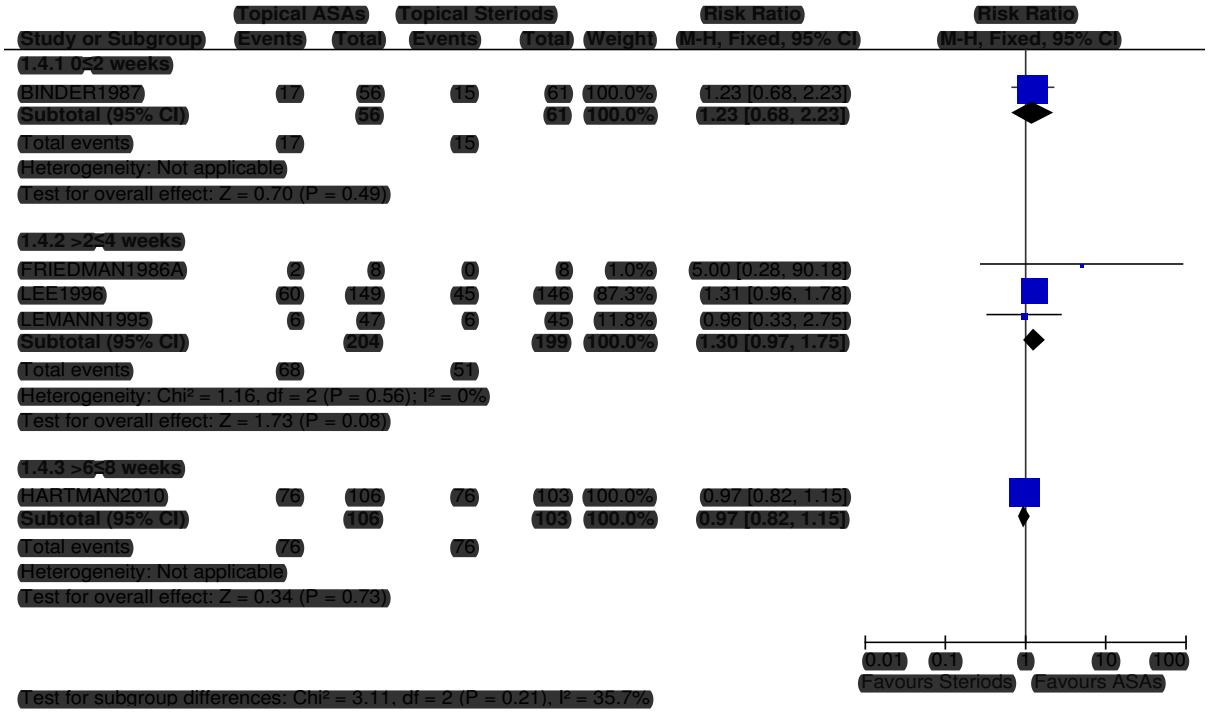


Figure 72: Clinical and endoscopic remission

Figure 73: Adverse events

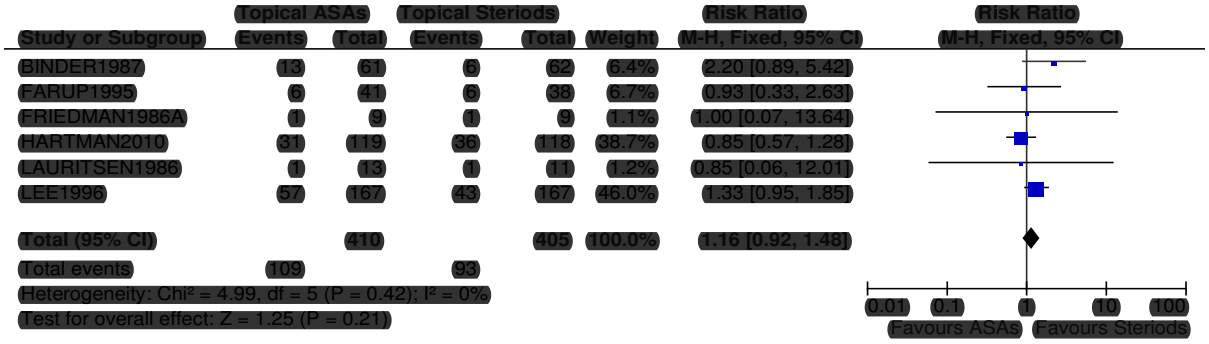


Figure 74: Serious adverse events

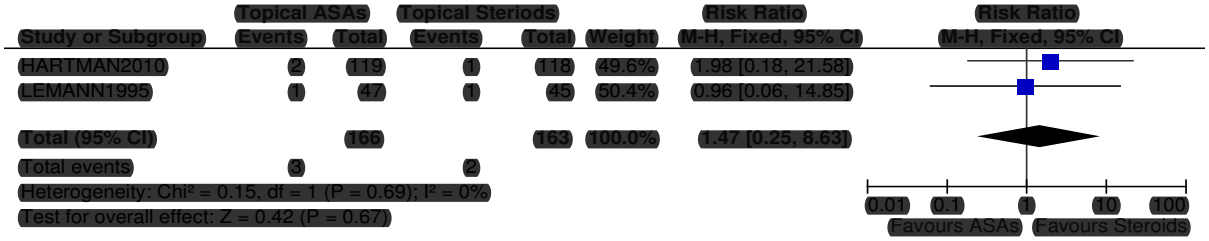
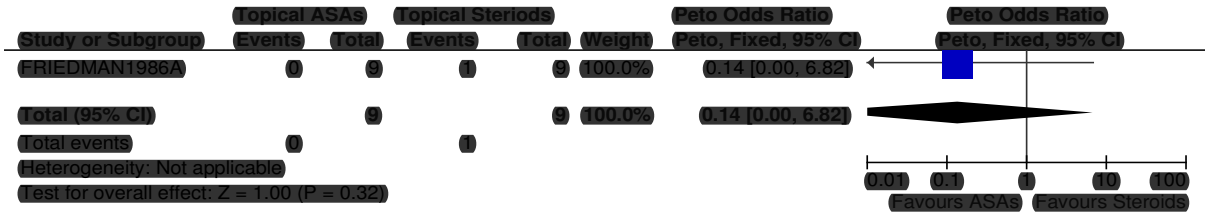


Figure 75: Hospitalisations

Figure 76: Colectomy



1.1.6 Oral aminosalicylates

1.1.6.1 Oral aminosalicylates versus placebo

Figure 77: Clinical remission

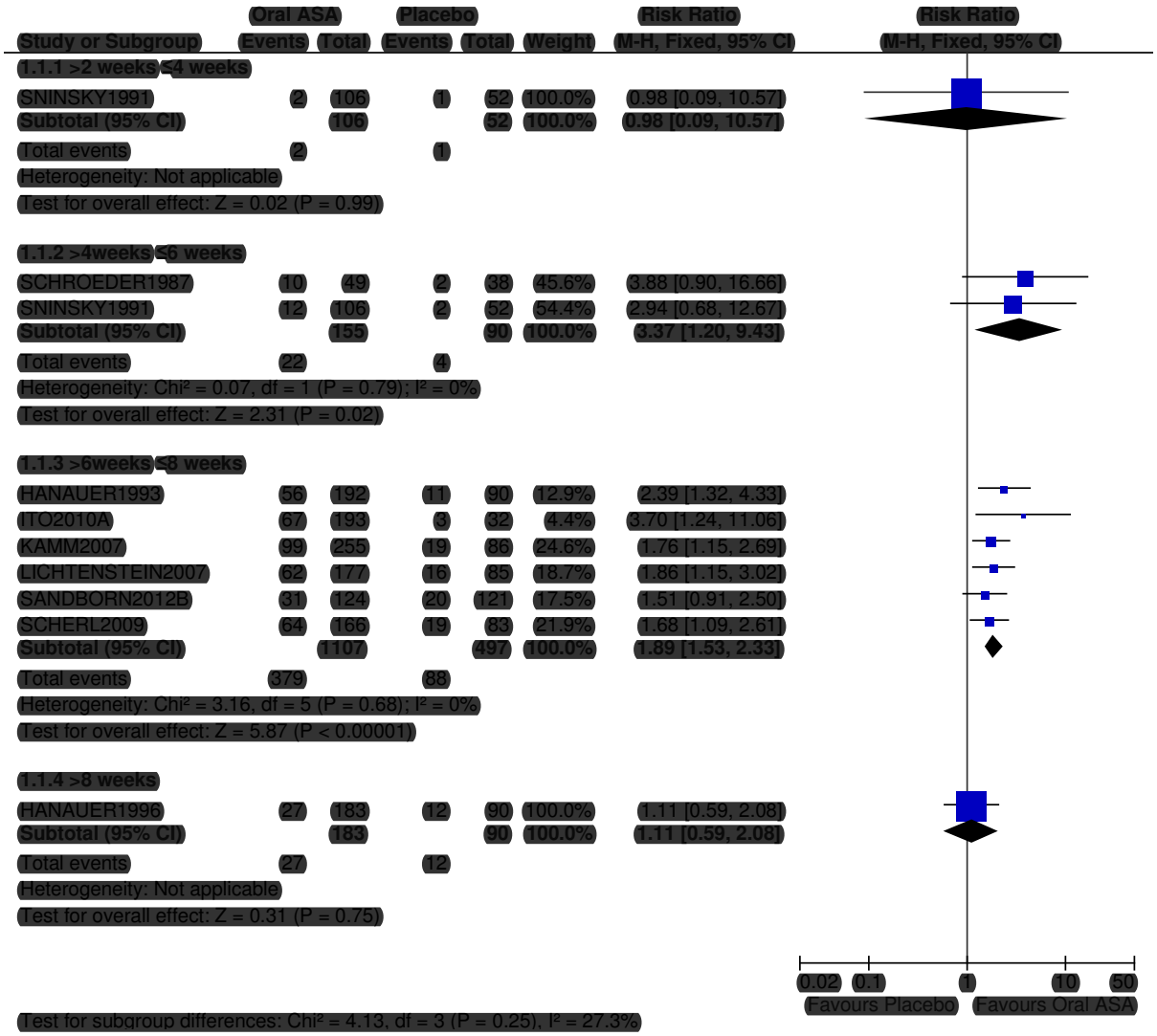


Figure 78: Clinical improvement

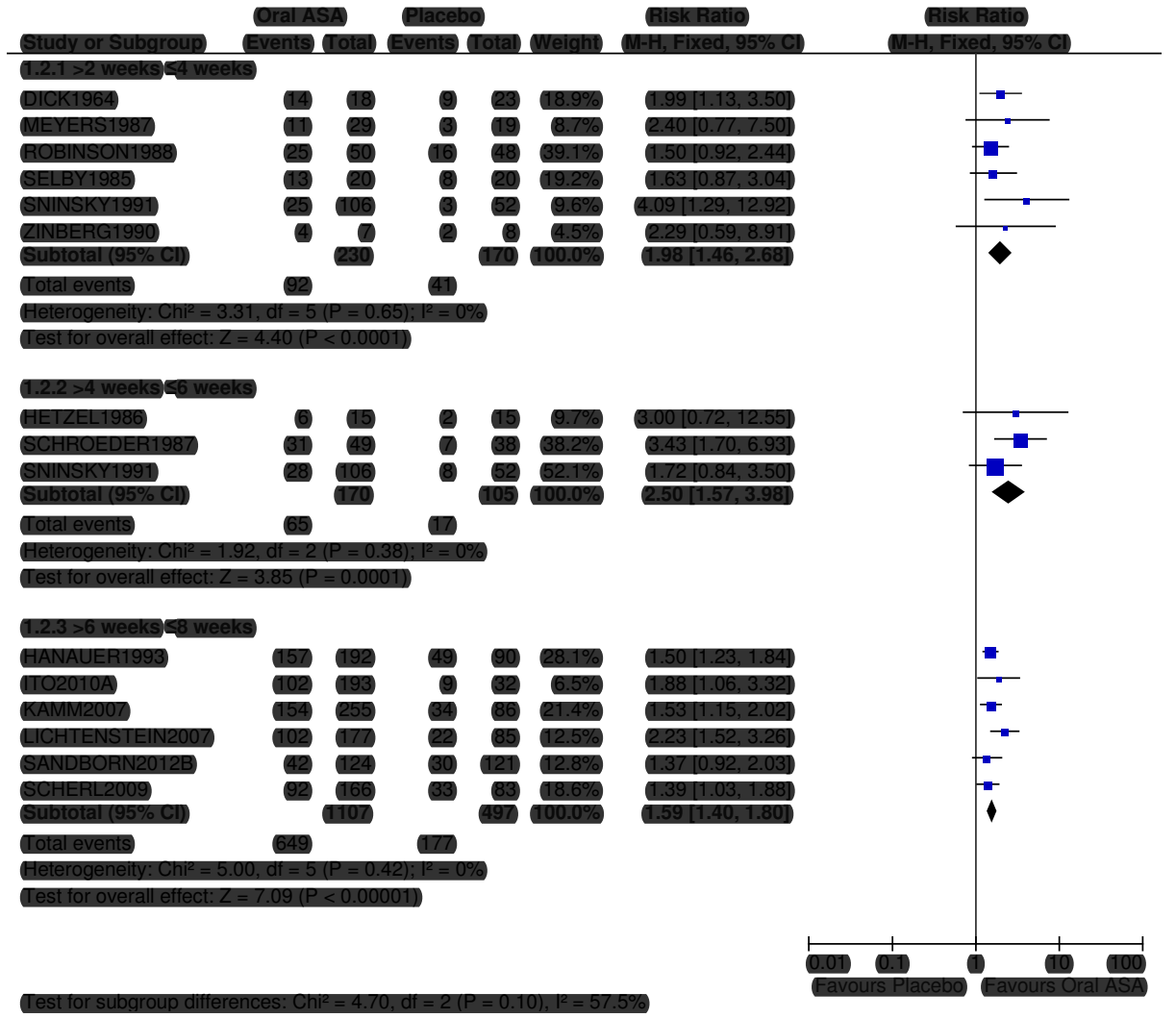


Figure 79: Endoscopic remission

Figure 80: Clinical and endoscopic remission

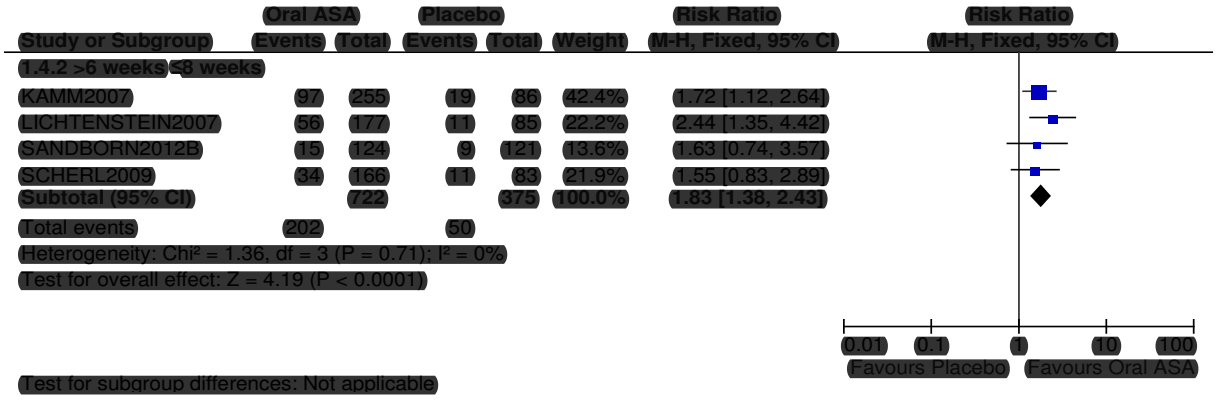


Figure 81: Adverse events

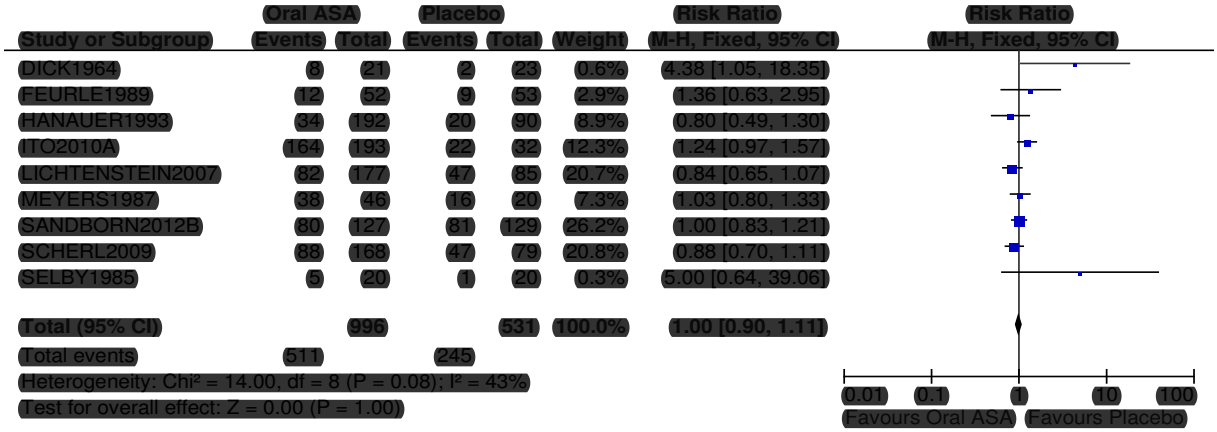
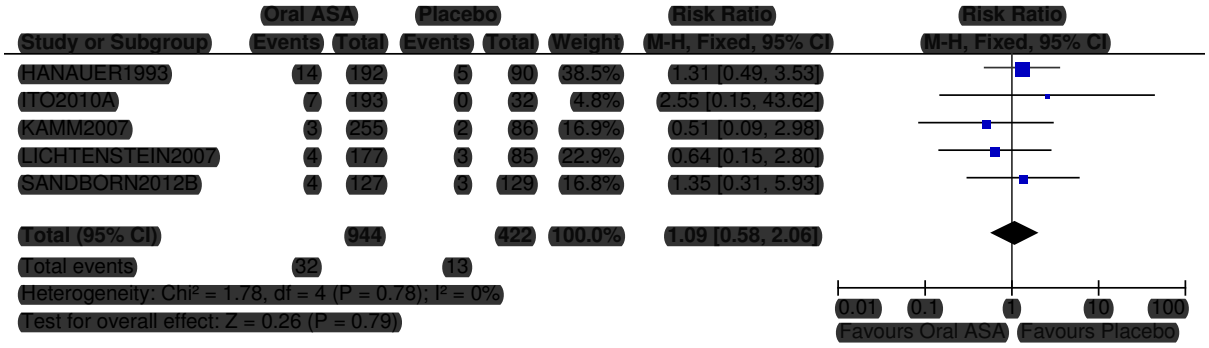


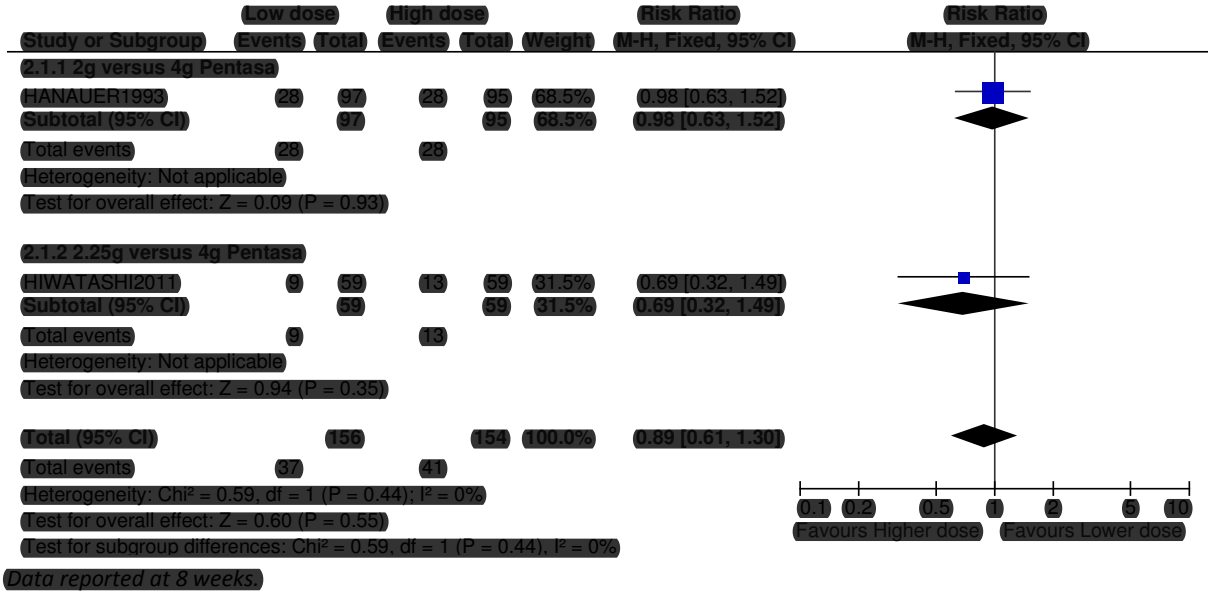
Figure 82: Serious adverse events



1.1.7 Oral aminosalicylate versus oral aminosalicylate: dose comparison

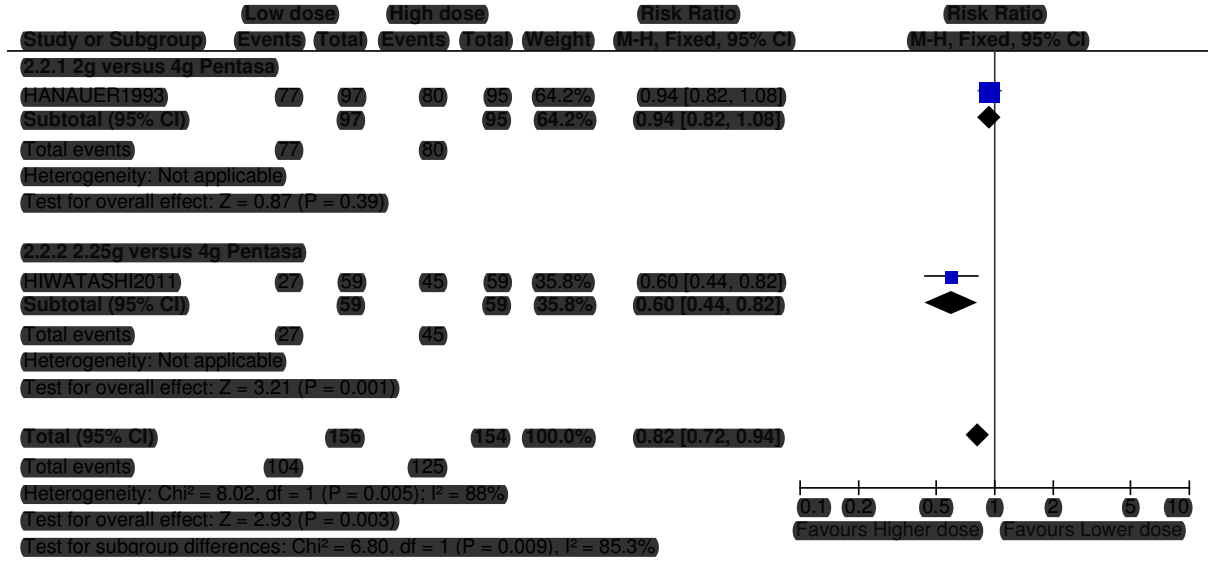
1.1.7.1 Mesalazine (Pentasa)

Figure 83: Clinical remission



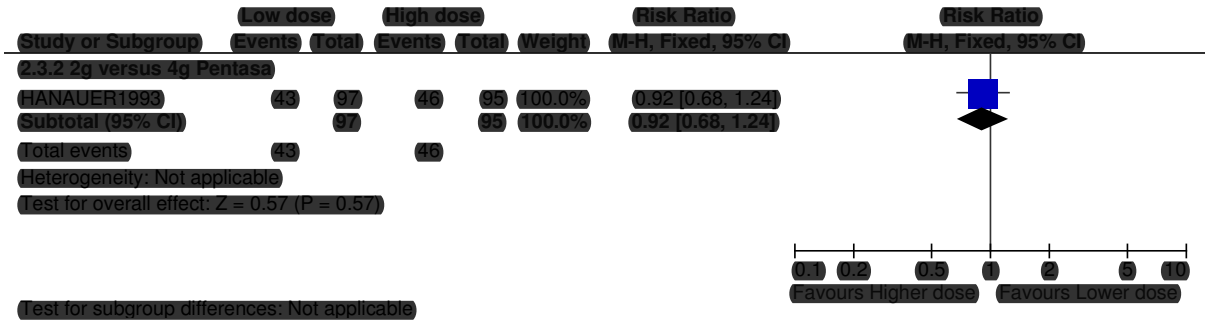
Data reported at 8 weeks.

Figure 84: Clinical improvement



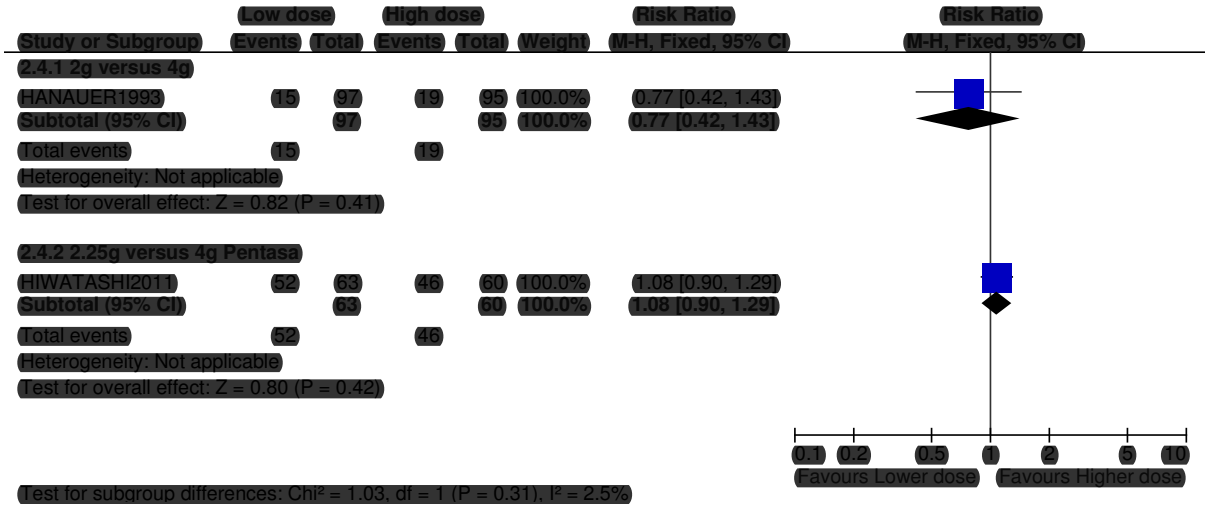
Data reported at 8 weeks.

Figure 85: Endoscopic remission



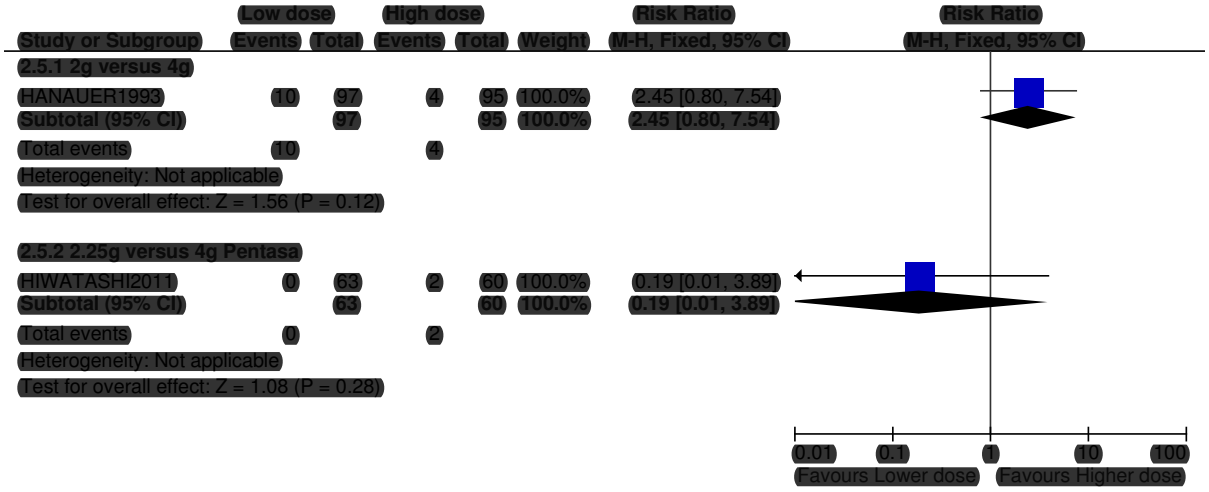
Data reported at 8 weeks.

Figure 86: Adverse events



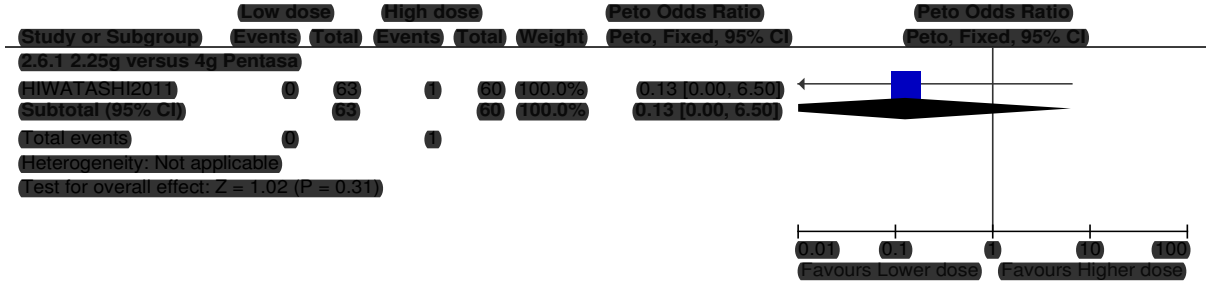
Data reported at 8 weeks.

Figure 87: Serious adverse events



Data reported at 8 weeks.

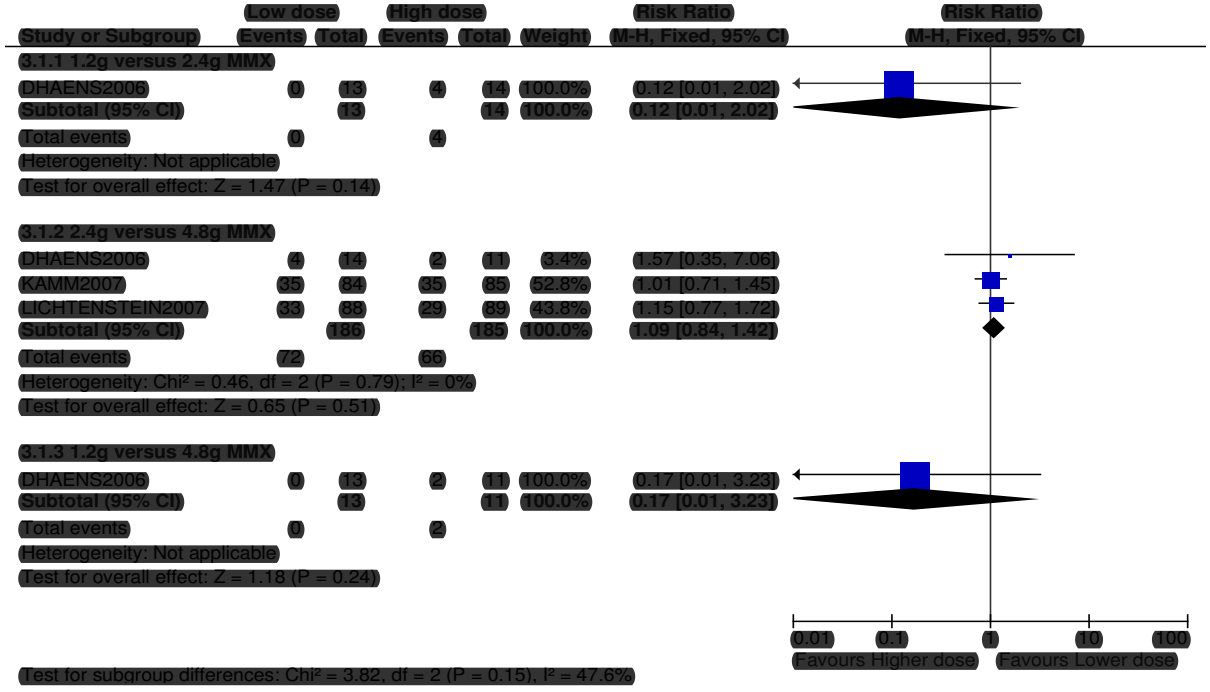
Figure 88: Hospitalisations



Data reported at 8 weeks.

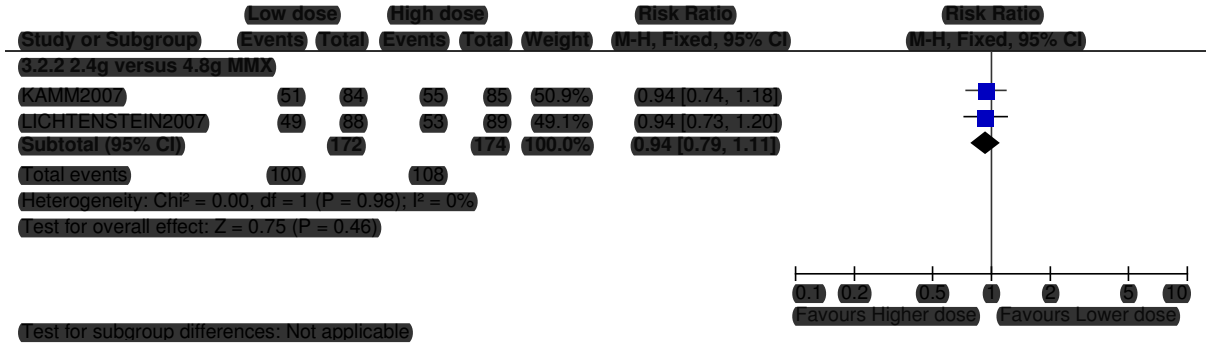
1.1.7.2 Mesalazine (MEZAVANT XL)

Figure 89: Clinical remission



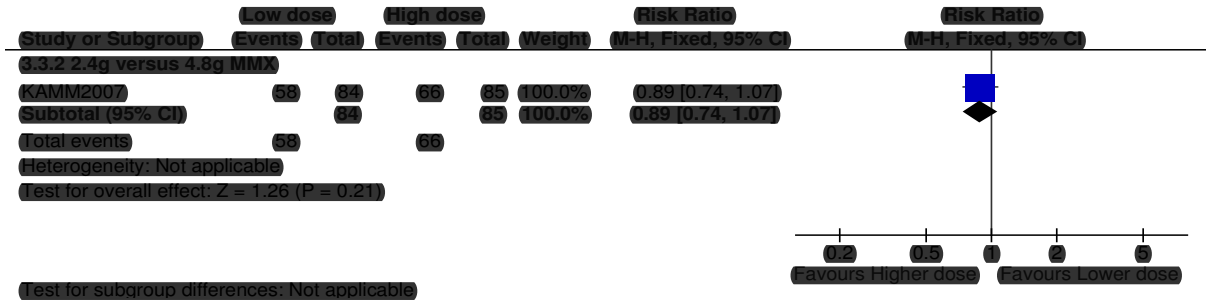
Data reported at 8 weeks.

Figure 90: Clinical improvement



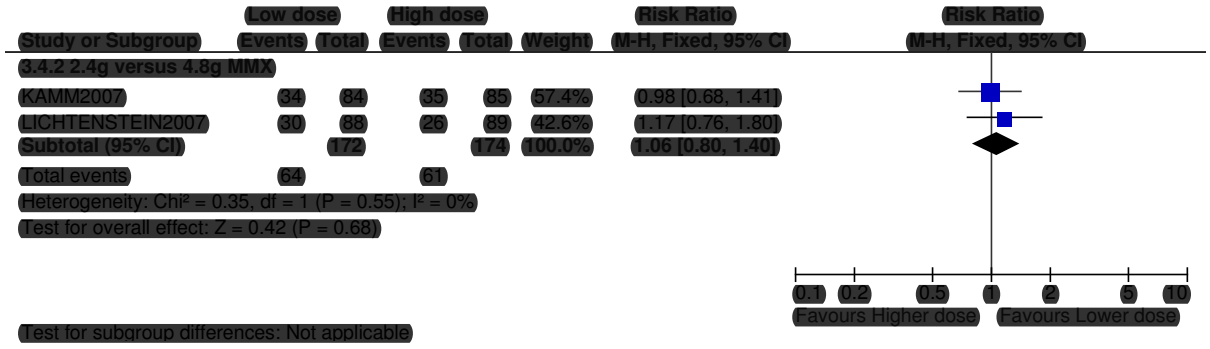
Data reported at 8 weeks.

Figure 91: Endoscopic remission



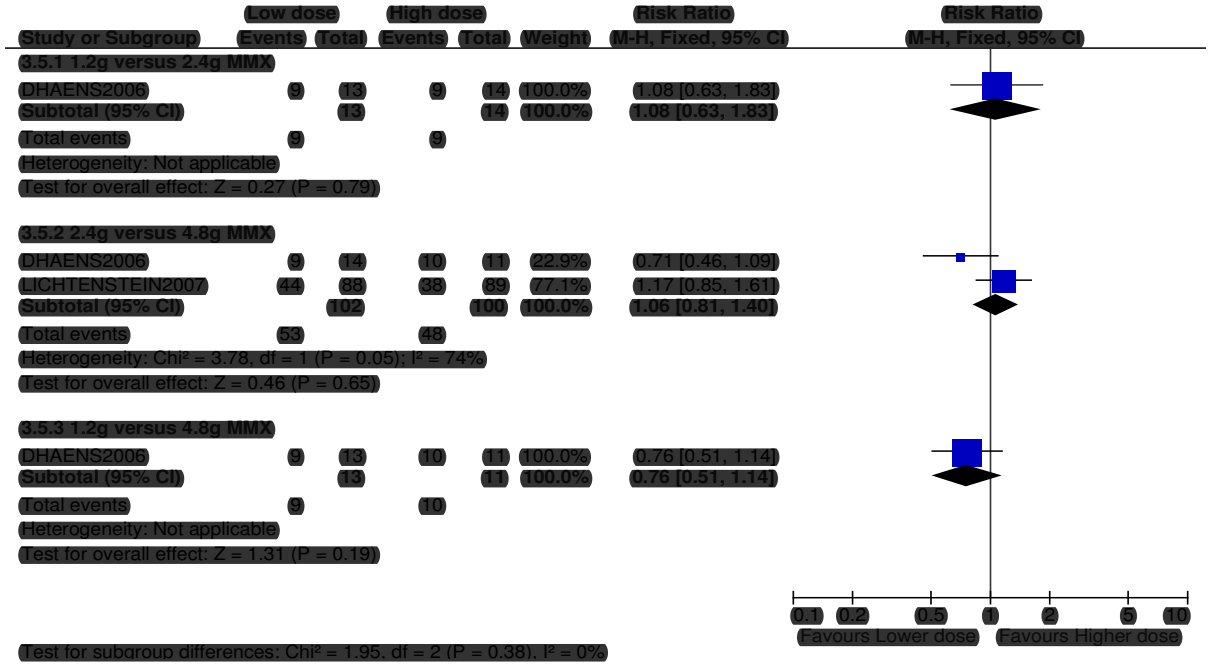
Data reported at 8 weeks.

Figure 92: Clinical and endoscopic remission



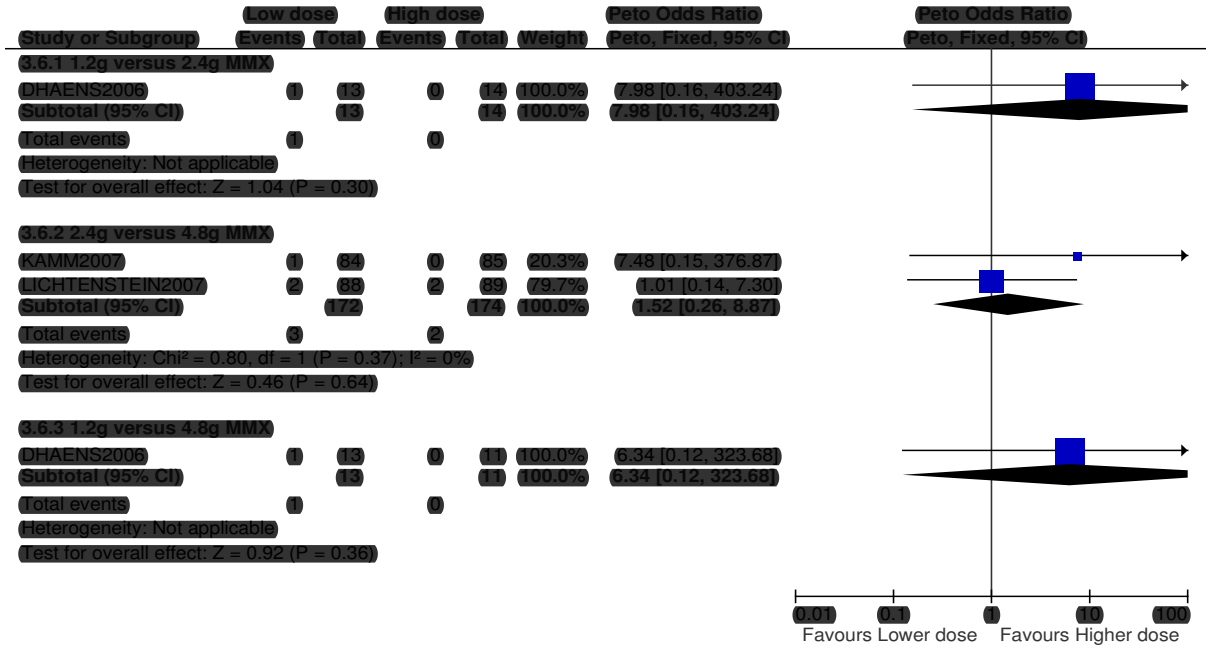
Data reported at 8 weeks.

Figure 93: Adverse events



Data reported at 8 weeks.

Figure 94: Serious adverse events



Data reported at 8 weeks.

1.1.7.3 Mesalazine (Asacol)

Figure 95: Clinical remission

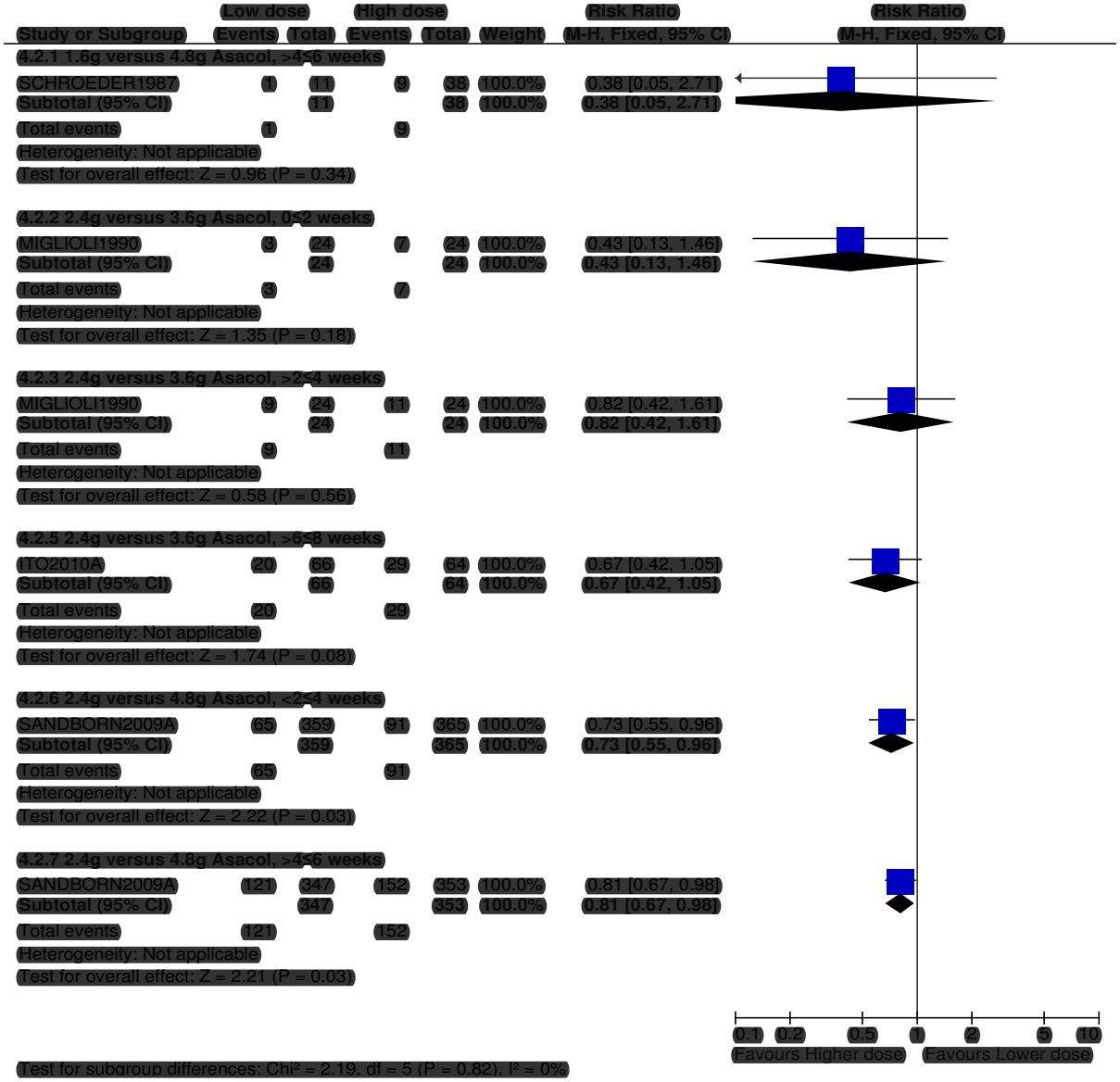


Figure 96: Clinical improvement

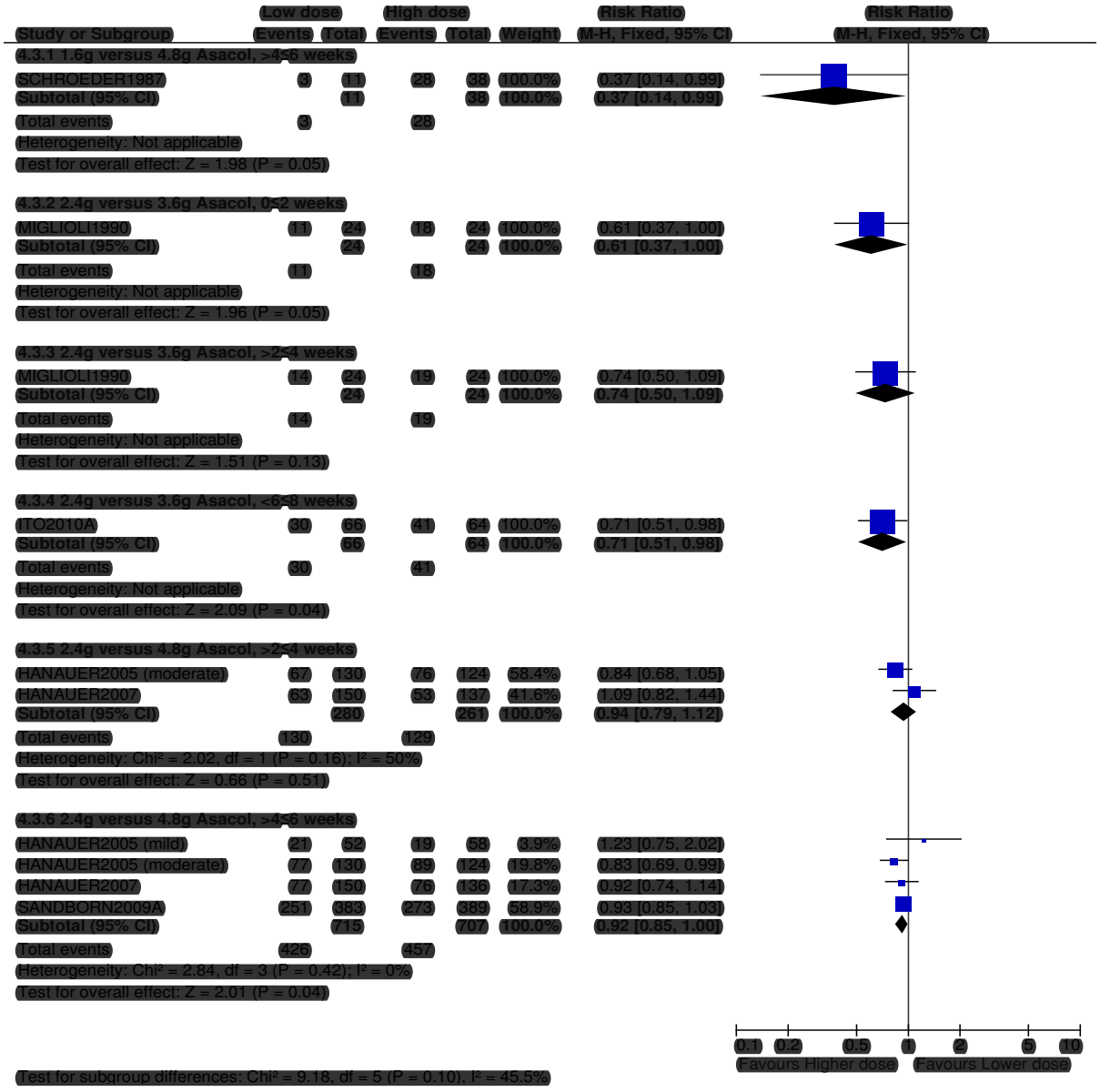
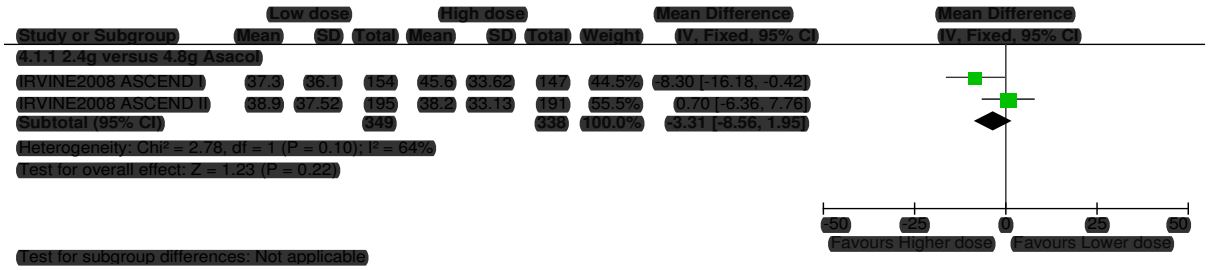
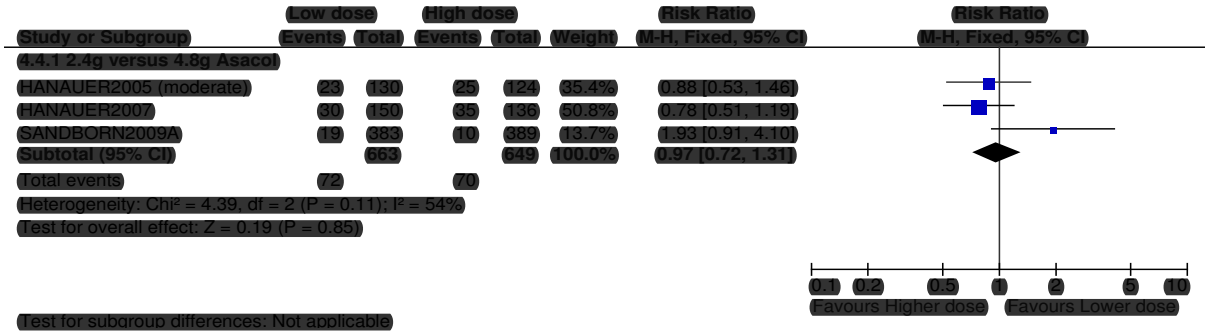


Figure 97: Quality of life



Data reported at baseline and 6 weeks.

Figure 98: Clinical and endoscopic remission, fixed effects



Data reported at 6 weeks.

Figure 99: Clinical and endoscopic remission, random effects

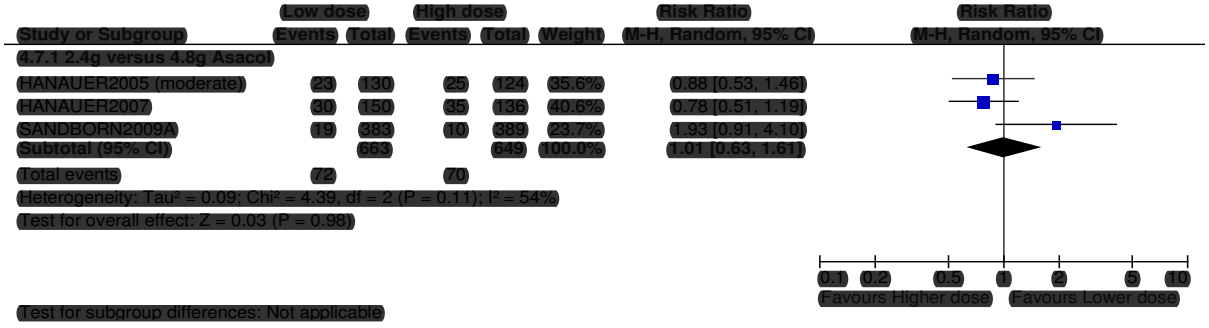


Figure 100: Clinical and endoscopic remission, 2.4g versus 4.8g Asacol, by severity of disease

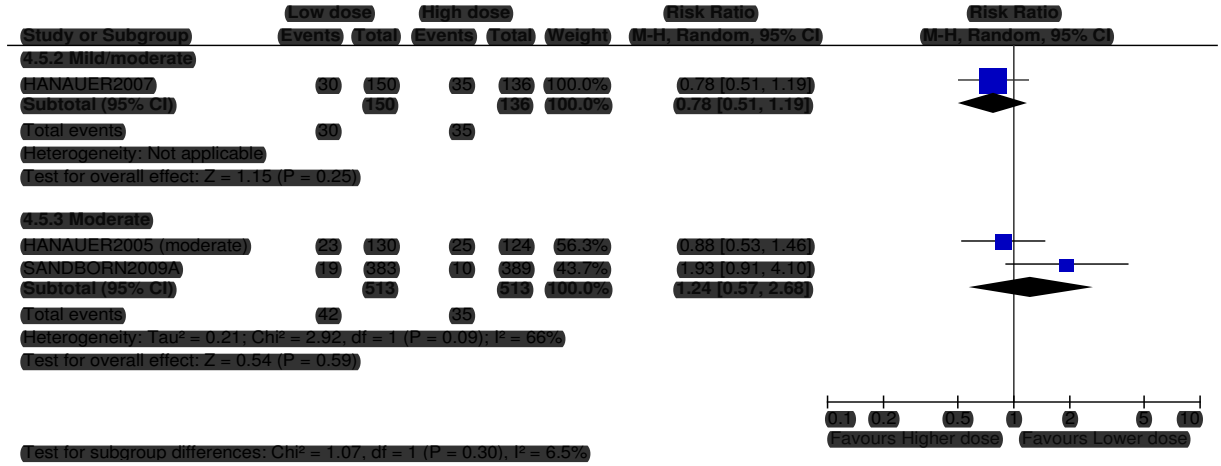


Figure 101: Clinical and endoscopic remission, 2.4g versus 4.8g Asacol, by extent of disease

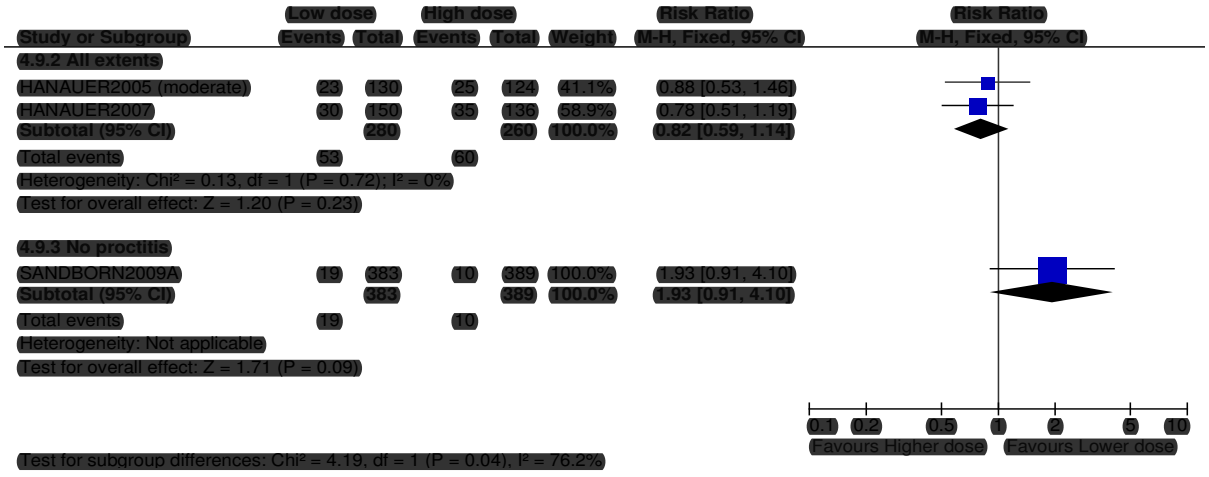
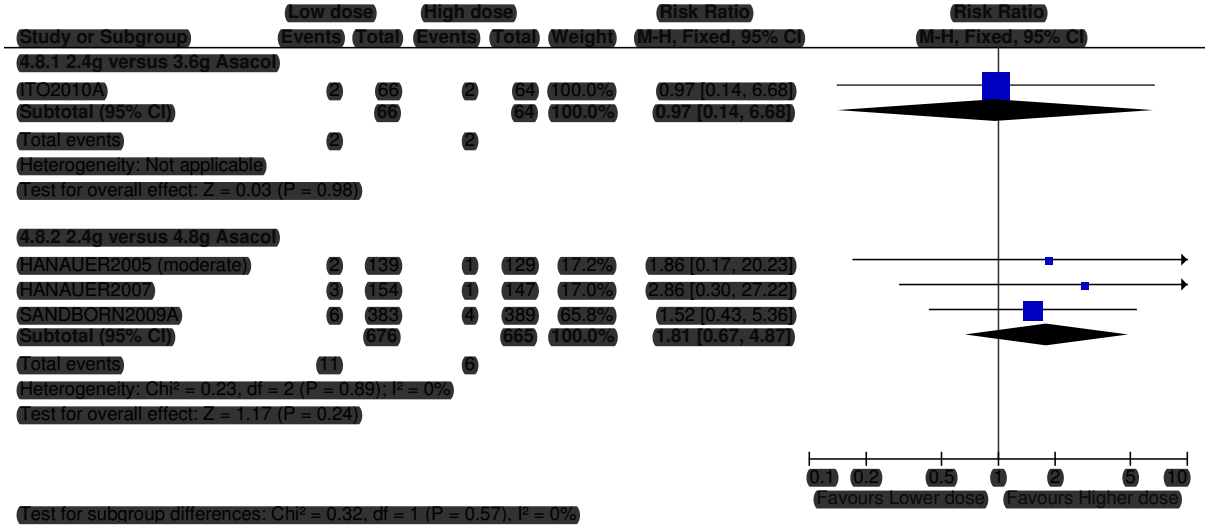


Figure 102: Adverse events

Figure 103: Serious adverse events



1.1.7.4 Mesalazine (Salofalk)

Figure 104: Clinical remission

Data reported at 8 weeks.

Figure 105: Clinical improvement

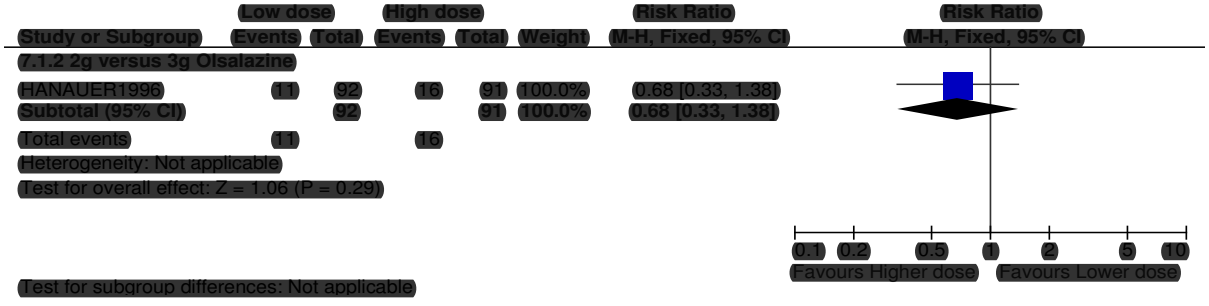
Data reported at 8 weeks

Figure 106: Adverse events

Data reported at 8 weeks.

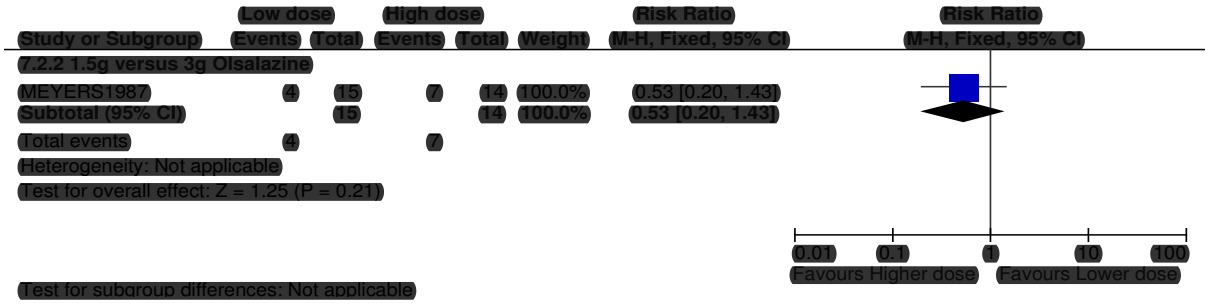
1.1.7.5 Olsalazine

Figure 107: Clinical remission



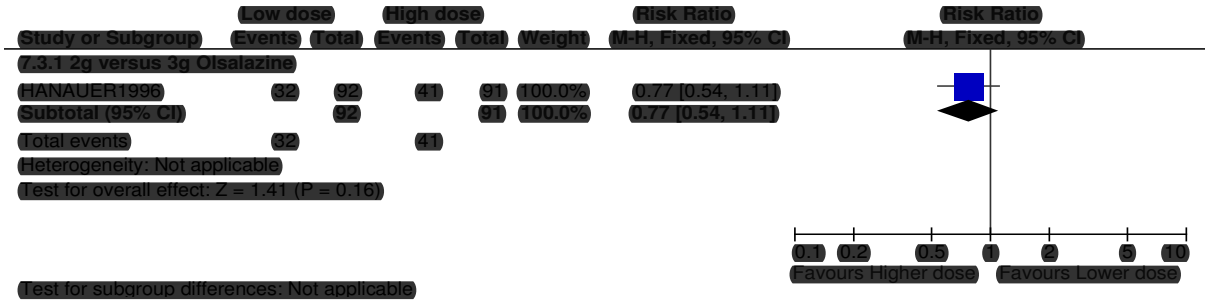
Data reported at 12 weeks.

Figure 108: Clinical improvement



Data reported at 3 weeks.

Figure 109: Endoscopic remission

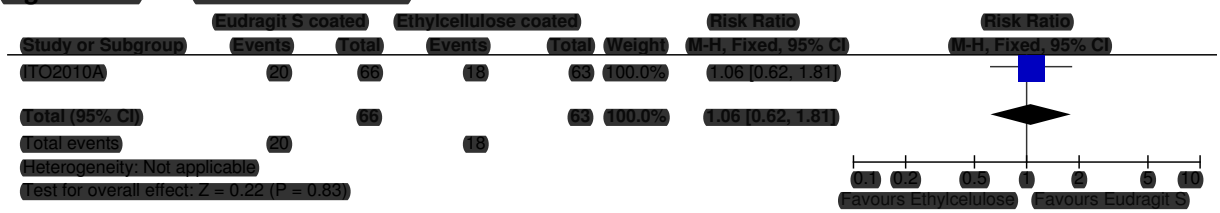


Data reported at 12 weeks.

1.1.8 Interclass comparison

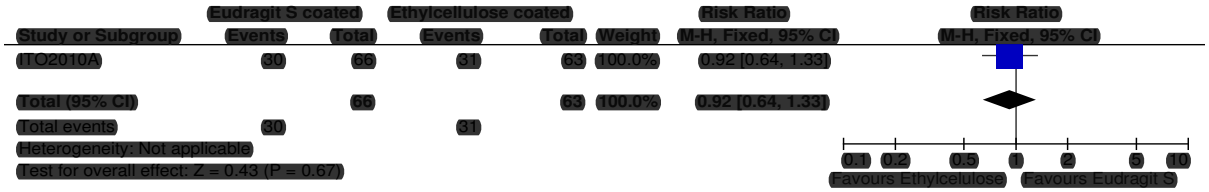
1.1.8.1 Mesalazine comparison: Eudragit S 2.4g (400mg Asacol) versus Ethylcellulose (Pentasa) 2.25g

Figure 110: Clinical remission



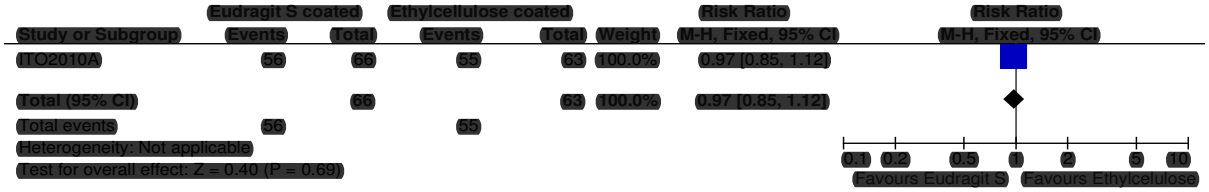
Data reported at 8 weeks.

Figure 111: Clinical improvement



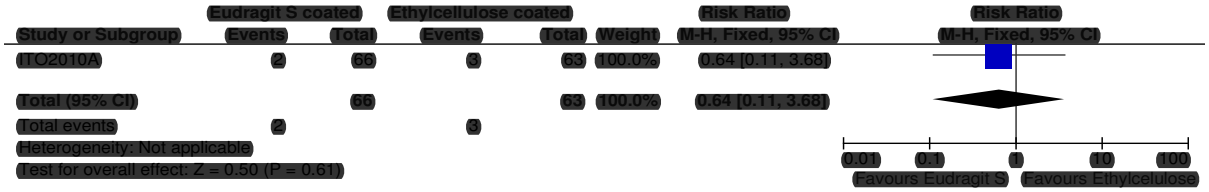
Data reported at 8 weeks.

Figure 112: Adverse events



Data reported at 8 weeks.

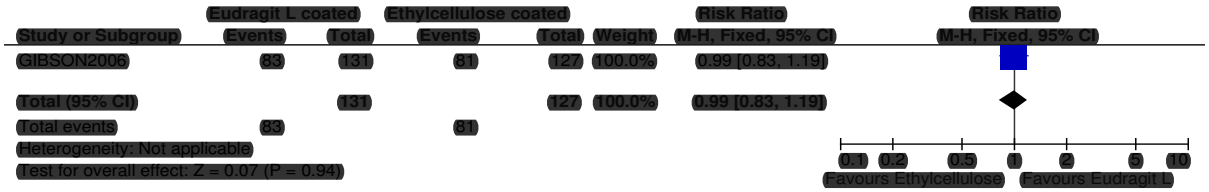
Figure 113: Serious adverse events



Data reported at 8 weeks.

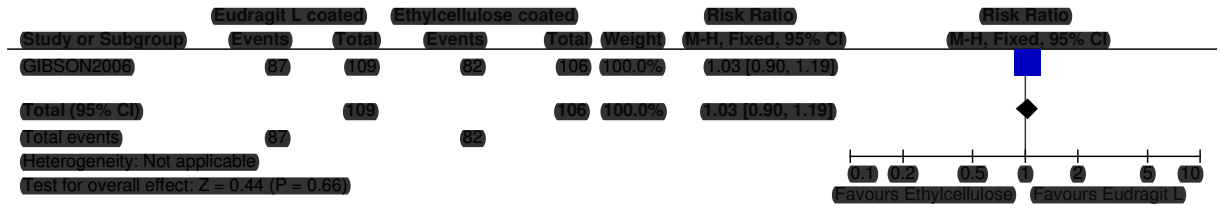
1.1.8.2 Mesalazine comparison: Eudragit L coated mesalazine (3g Salofalk) versus ethylcellulose coated mesalazine (3g)

Figure 114: Clinical remission



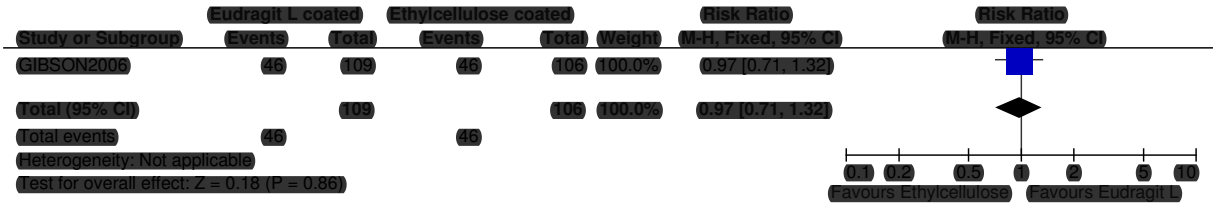
Data reported at 8 weeks.

Figure 115: Clinical improvement



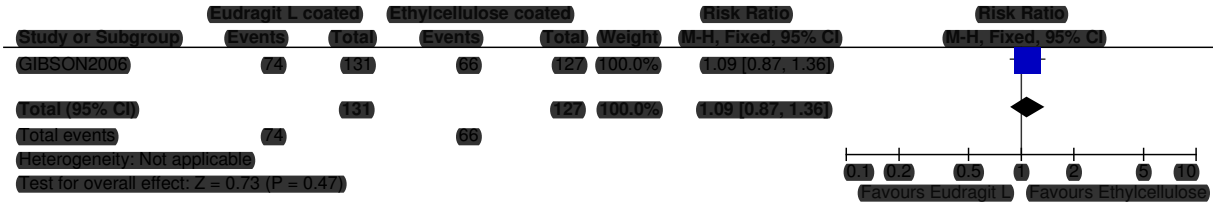
Data reported at 8 weeks.

Figure 116: Endoscopic remission



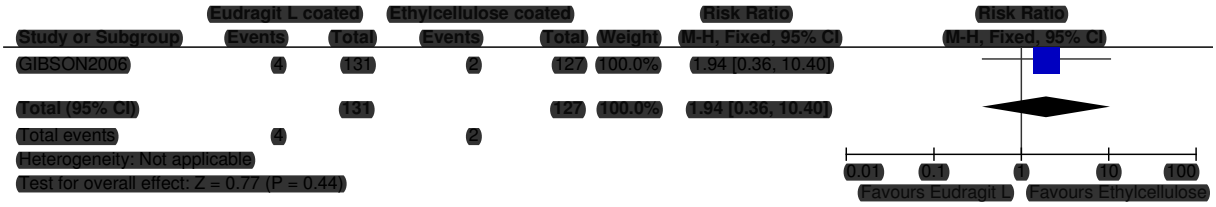
Data reported at 8 weeks.

Figure 117: Adverse events



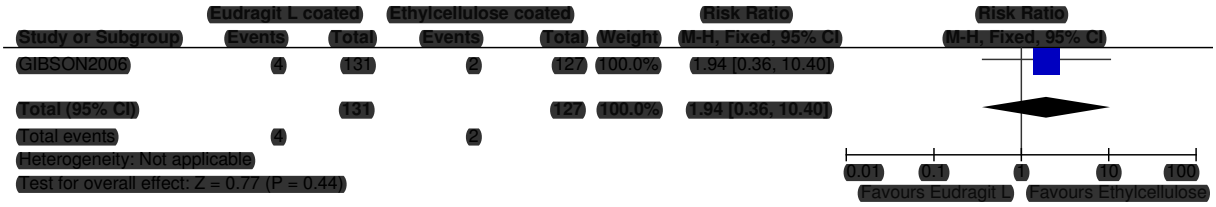
Data reported at 8 weeks.

Figure 118: Serious adverse events



Data reported at 8 weeks.

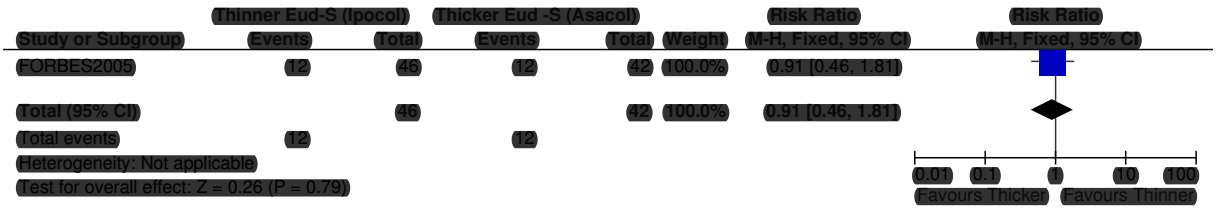
Figure 119: Hospitalisations



Data reported at 8 weeks.

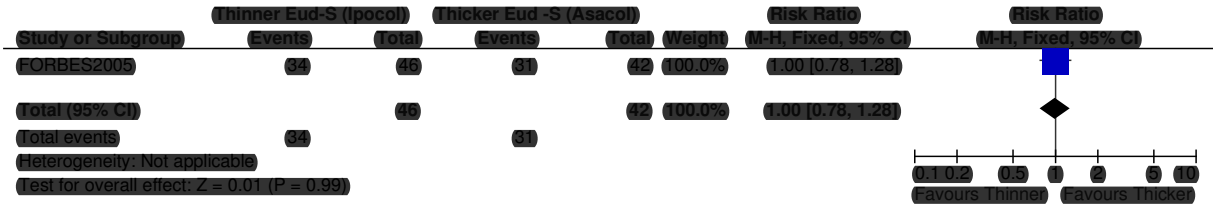
1.1.8.3 Mesalazine comparison: Eudragit S (Ipocol) versus Eudragit S (Asacol)

Figure 120: Clinical remission



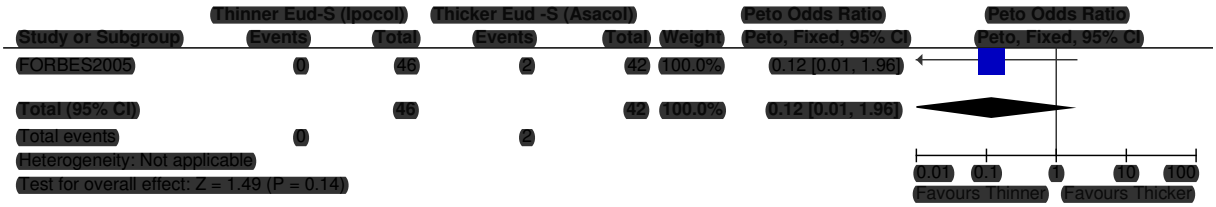
Data reported at 4 weeks.

Figure 121: Adverse events



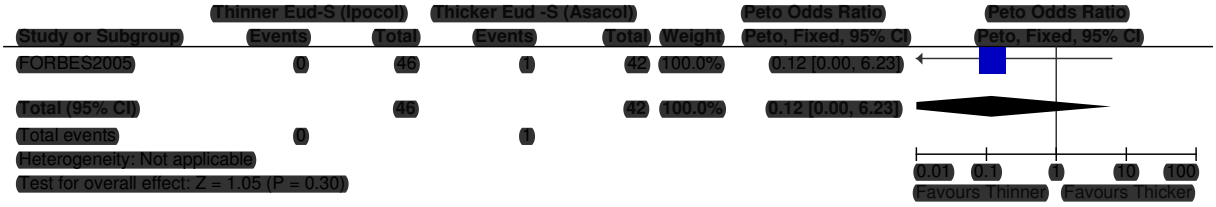
Data reported at 8 weeks.

Figure 122: Serious adverse events



Data reported at 8 weeks.

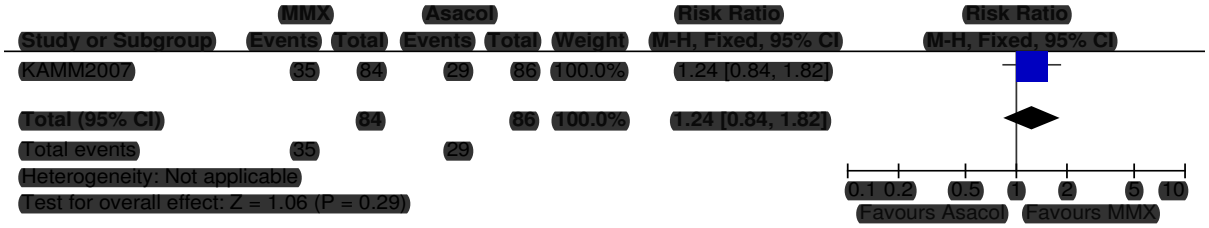
Figure 123: Colectomy



Data reported at 8 weeks.

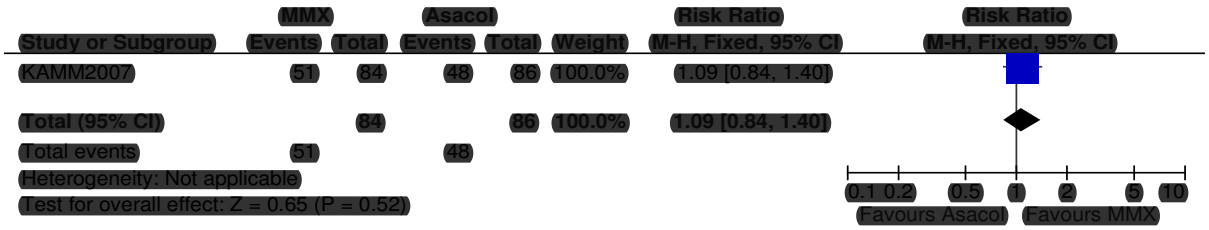
1.1.8.4 Mesalazine comparison: MEZAVANT XL versus Asacol

Figure 124: Clinical remission



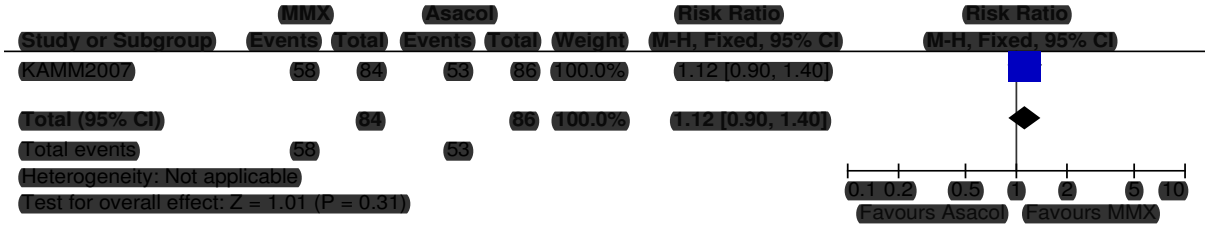
Data reported at 8 weeks.

Figure 125: Clinical improvement



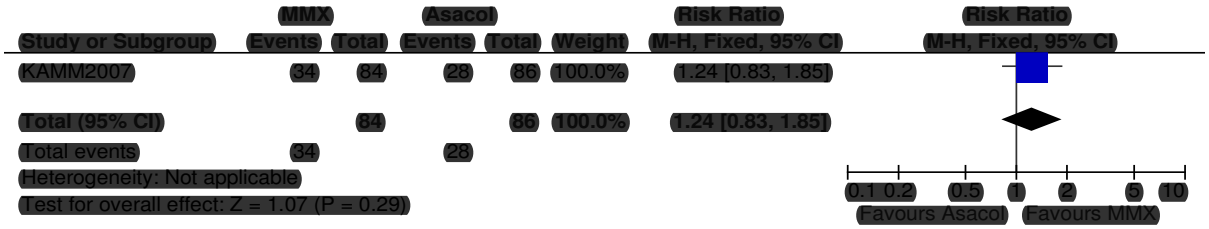
Data reported at 8 weeks.

Figure 126: Endoscopic remission



Data reported at 8 weeks.

Figure 127: Clinical and endoscopic remission



Data reported at 8 weeks.

Figure 128: Serious adverse events

Data reported at 8 weeks.

1.1.8.5 Olsalazine versus sulphasalazine

Figure 129: Clinical remission

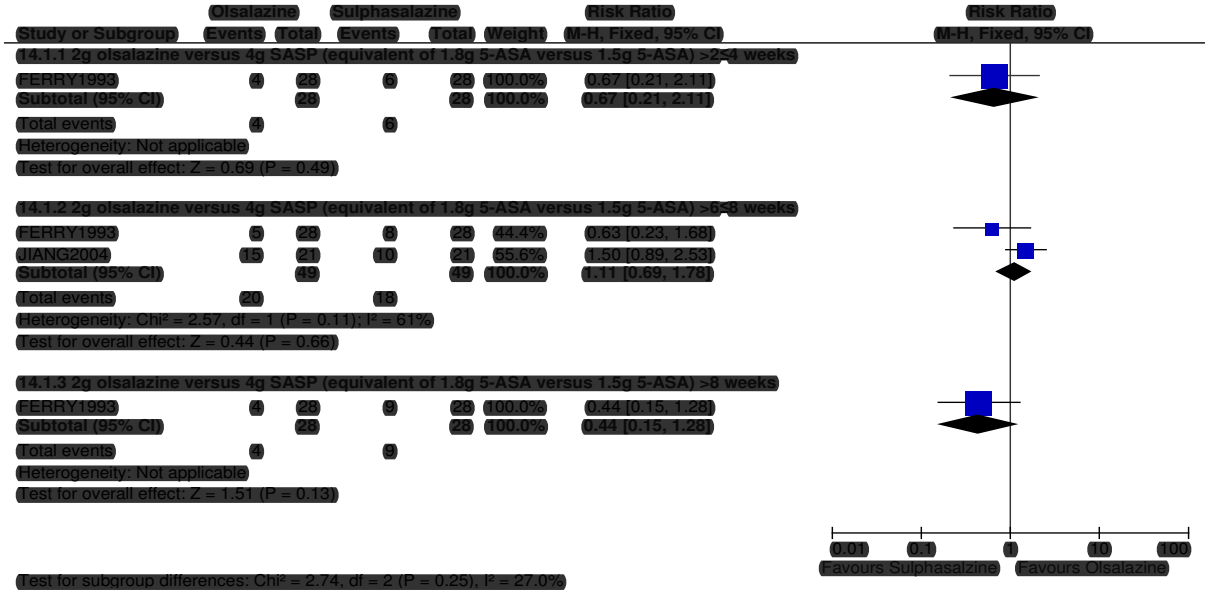


Figure 130: Clinical improvement

Figure 131: Endoscopic remission

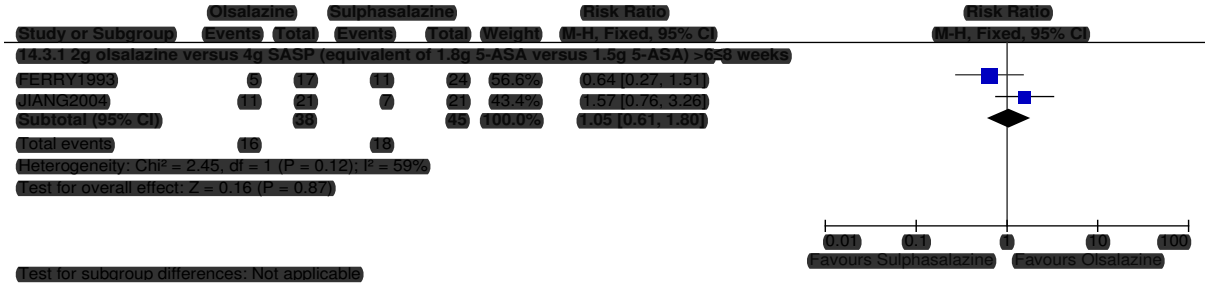


Figure 132: Clinical and endoscopic remission

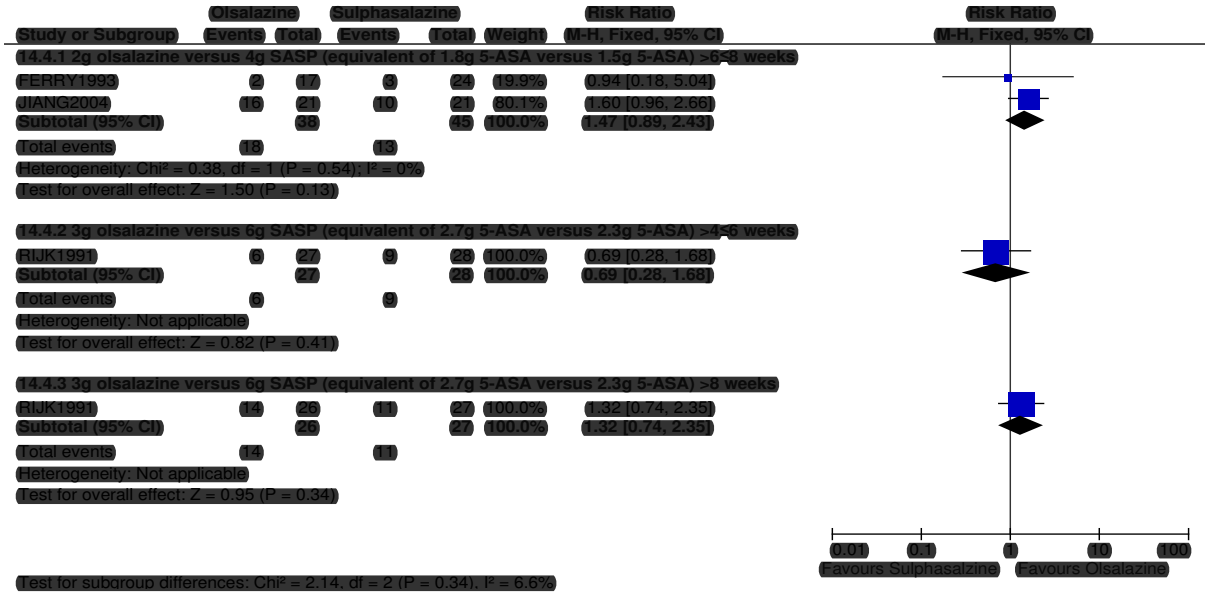
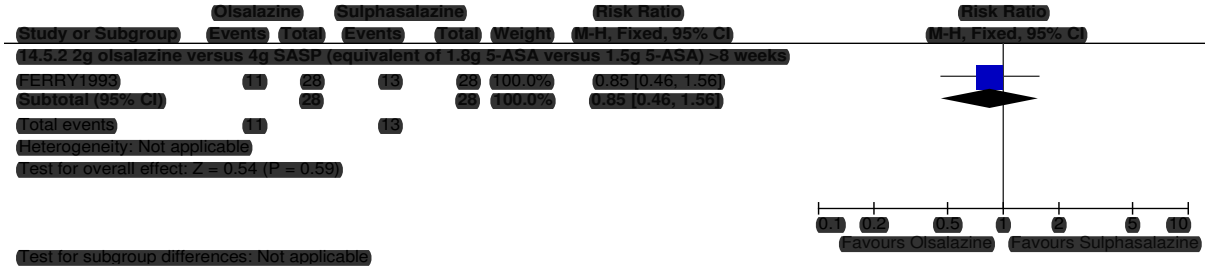


Figure 133: Adverse events



1.1.8.6 Balsalazide versus mesalazine (all types)

Figure 134: Clinical remission

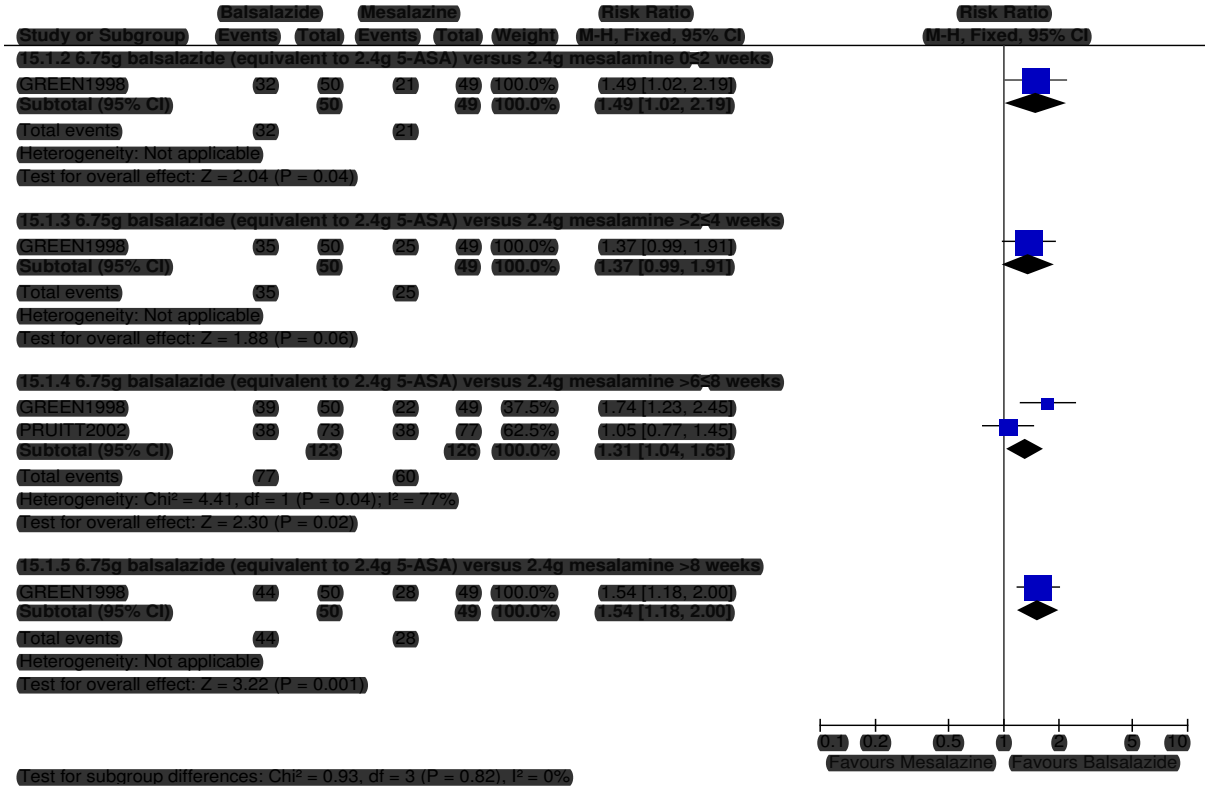


Figure 135: Clinical improvement

Figure 136: Clinical and endoscopic remission, fixed effects

Figure 137: Clinical and endoscopic remission at 8 weeks, random effects

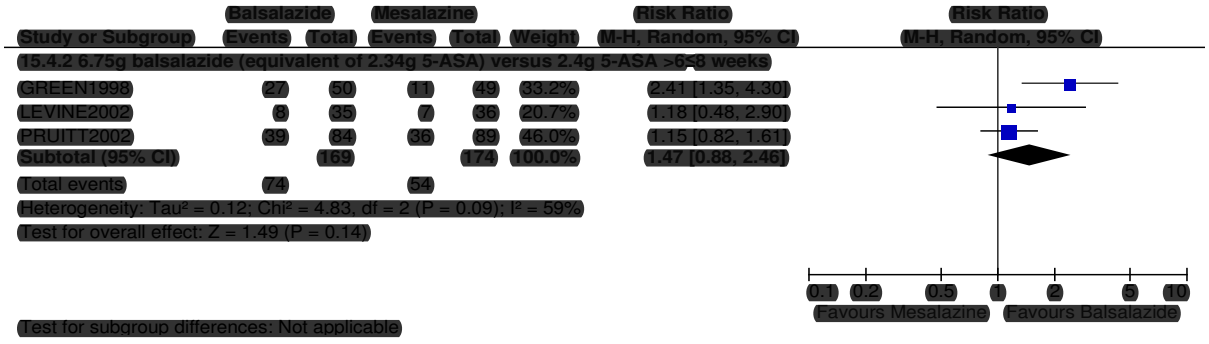
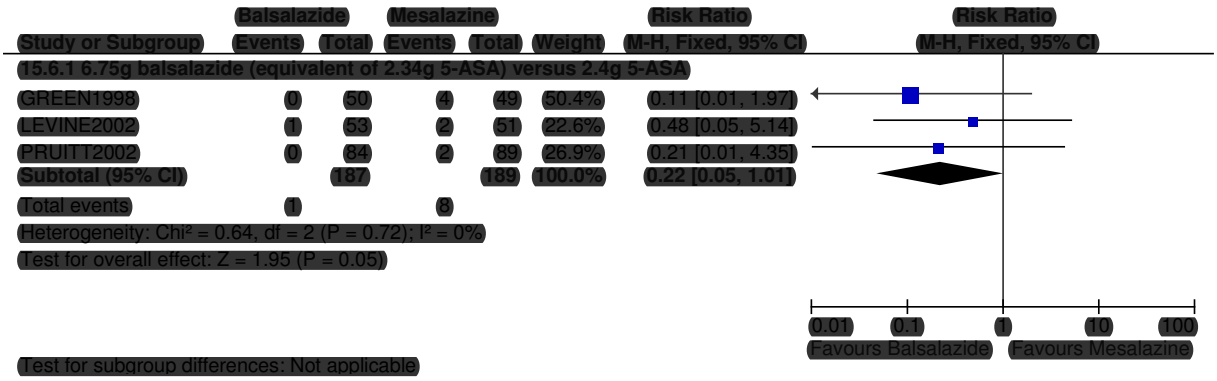


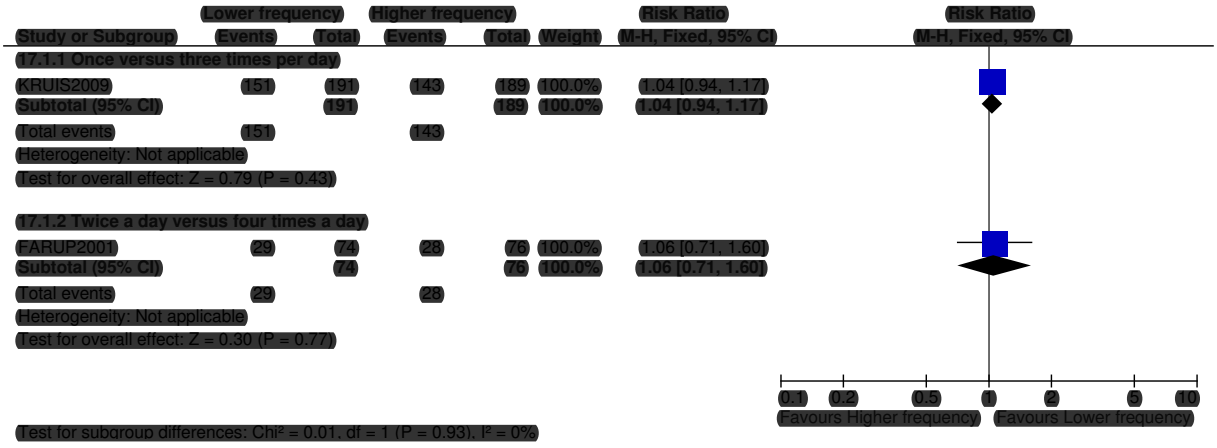
Figure 138: Adverse events

Figure 139: Serious adverse events



1.1.9 Oral aminosalicylates regimen comparison

Figure 140: Clinical remission

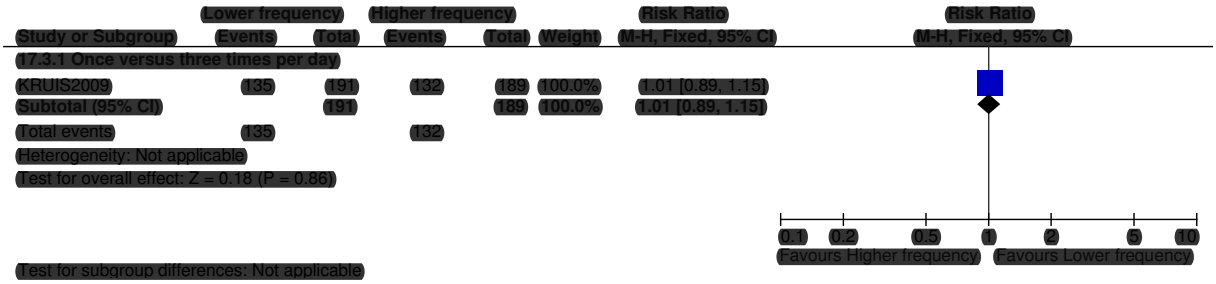


Data reported at 8 weeks.

Figure 141: Clinical improvement

Data reported at 8 weeks.

Figure 142: Endoscopic remission



Data reported at 8 weeks.

Figure 143: Adverse events

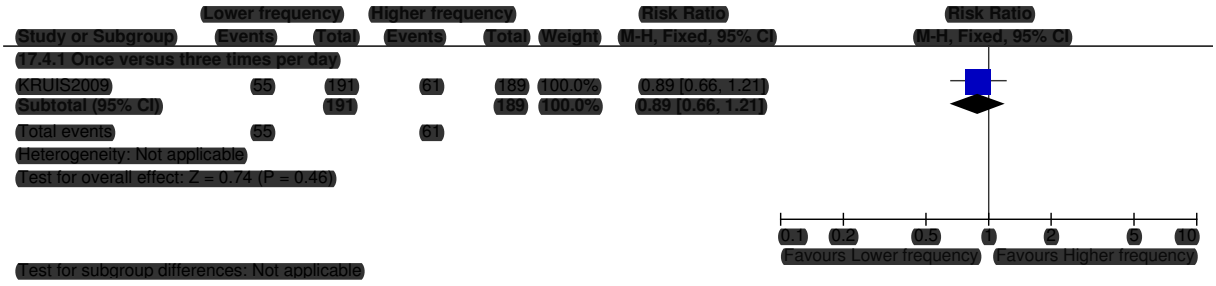
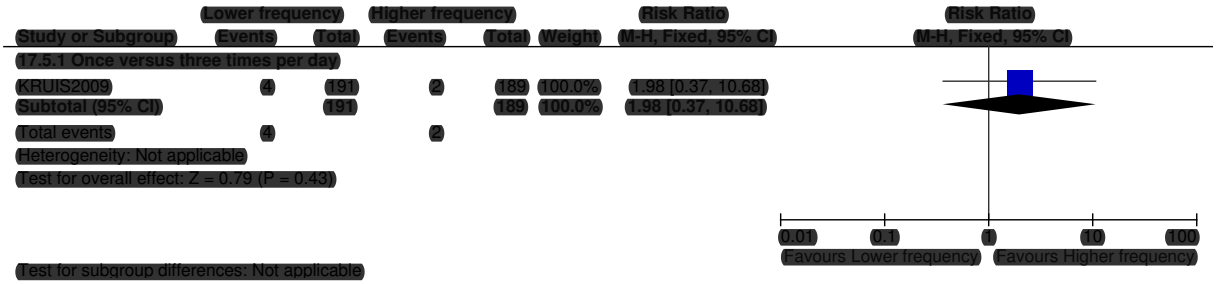


Figure 144: Serious adverse events



1.1.10 Oral aminosalicylates preparation comparison

1.1.10.1 Granules versus tablets (mesalazine)

Figure 145: Clinical remission

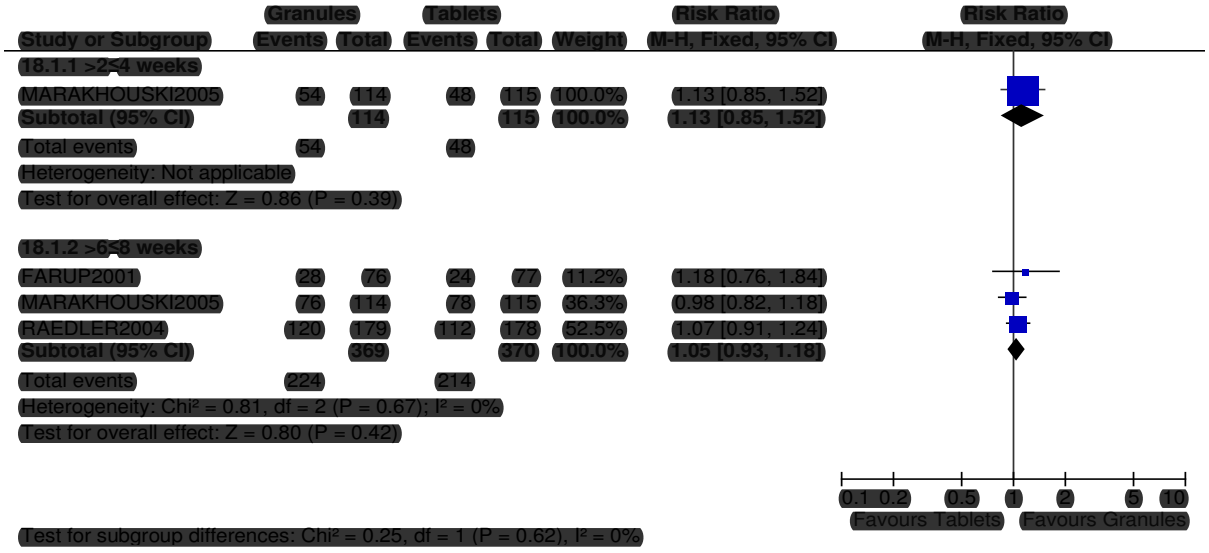
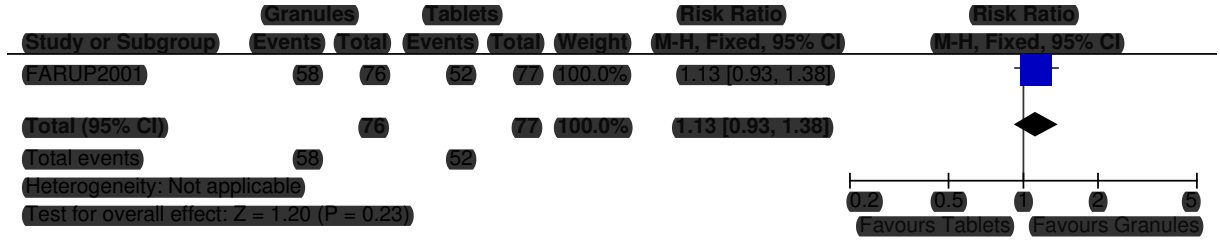
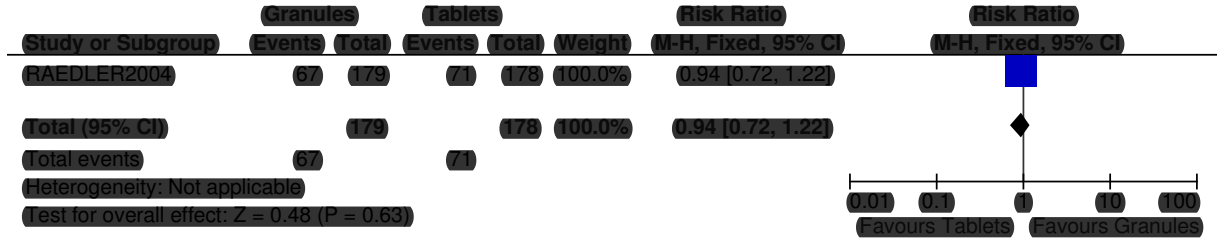


Figure 146: Clinical improvement, >6≤8 weeks



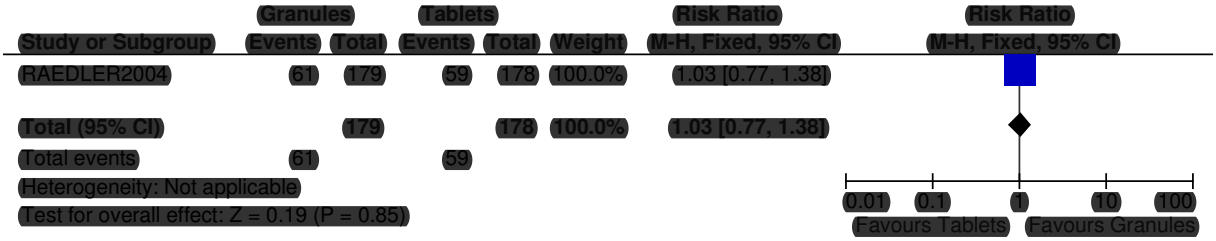
Data reported at 8 weeks.

Figure 147: Endoscopic remission, >6≤8 weeks



Data reported at 8 weeks.

Figure 148: Clinical and endoscopic remission, >6≤8 weeks



Data reported at 8 weeks.

Figure 149: Adverse events, fixed effects

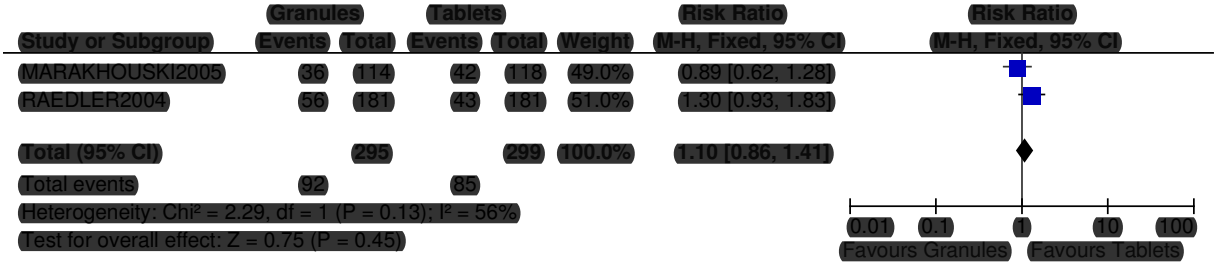


Figure 150: Adverse events, random effects

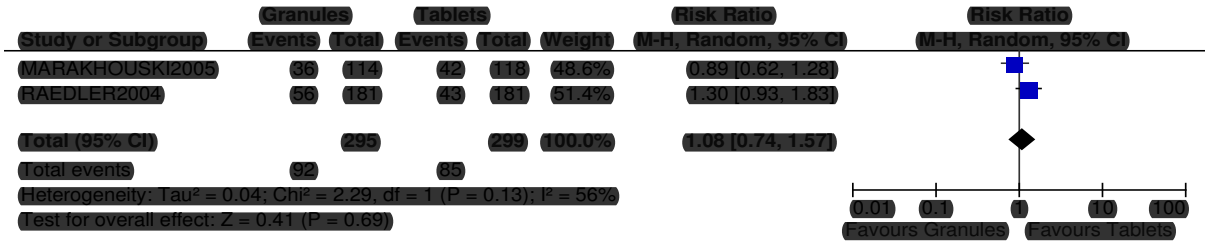
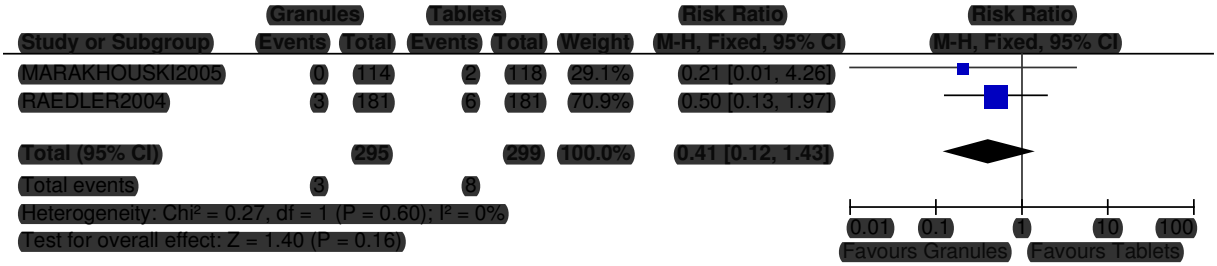


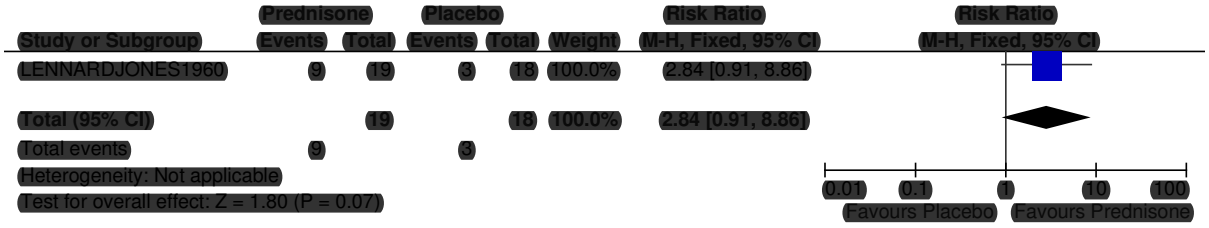
Figure 151: Serious adverse events



1.1.11 Oral corticosteroids

1.1.11.1 Oral corticosteroids versus placebo

Figure 152: Clinical and endoscopic remission



1.1.11.2 Oral corticosteroids dose comparison

1.1.11.3 Prednisolone

Figure 153: Clinical improvement (0≤2 weeks)

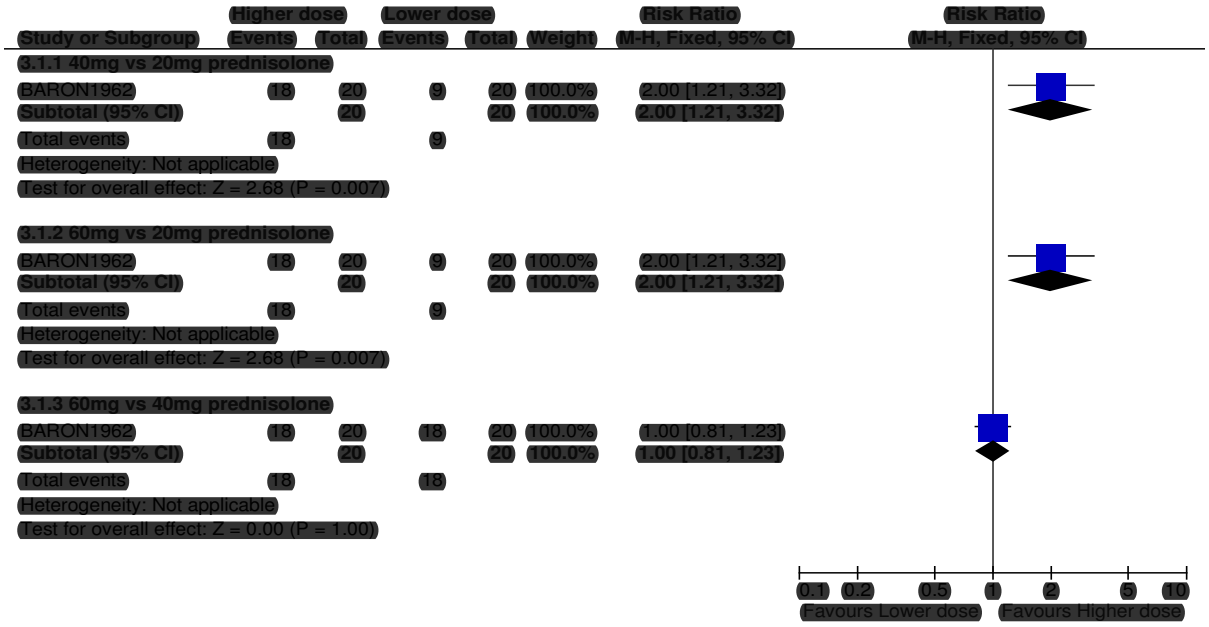


Figure 154: Clinical and endoscopic remission (0≤2 weeks)

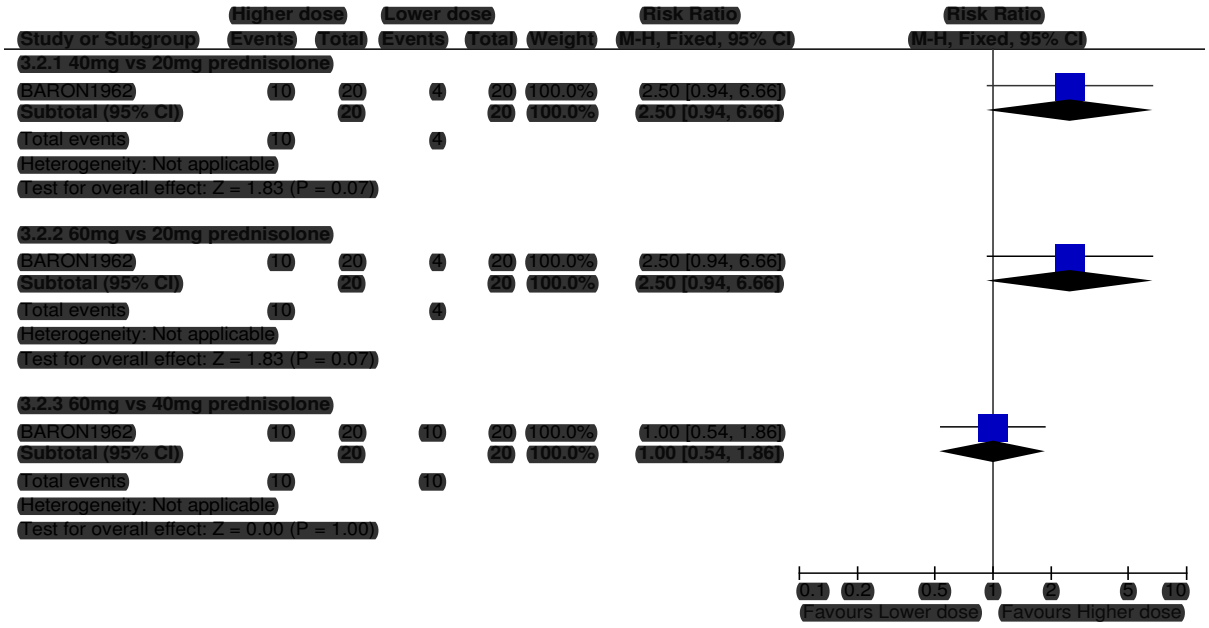
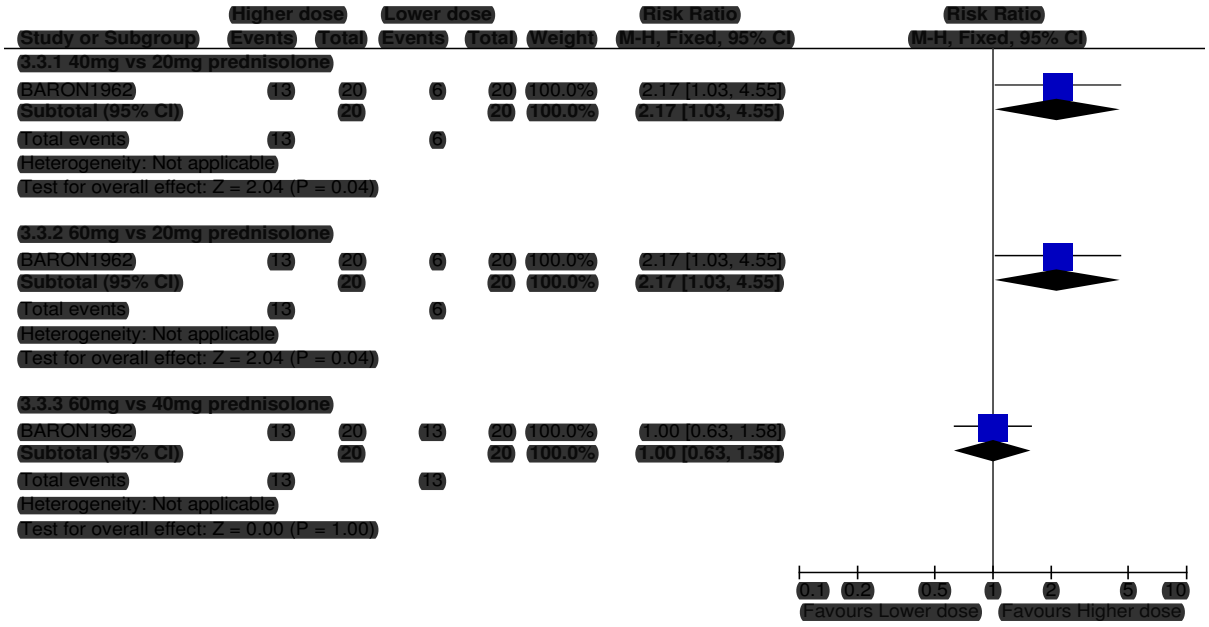


Figure 155: Clinical and endoscopic remission at the end of treatment



Note: Data reported at 5 weeks for 20,40mg and 3 weeks for 60mg

Figure 156: Hospitalisations

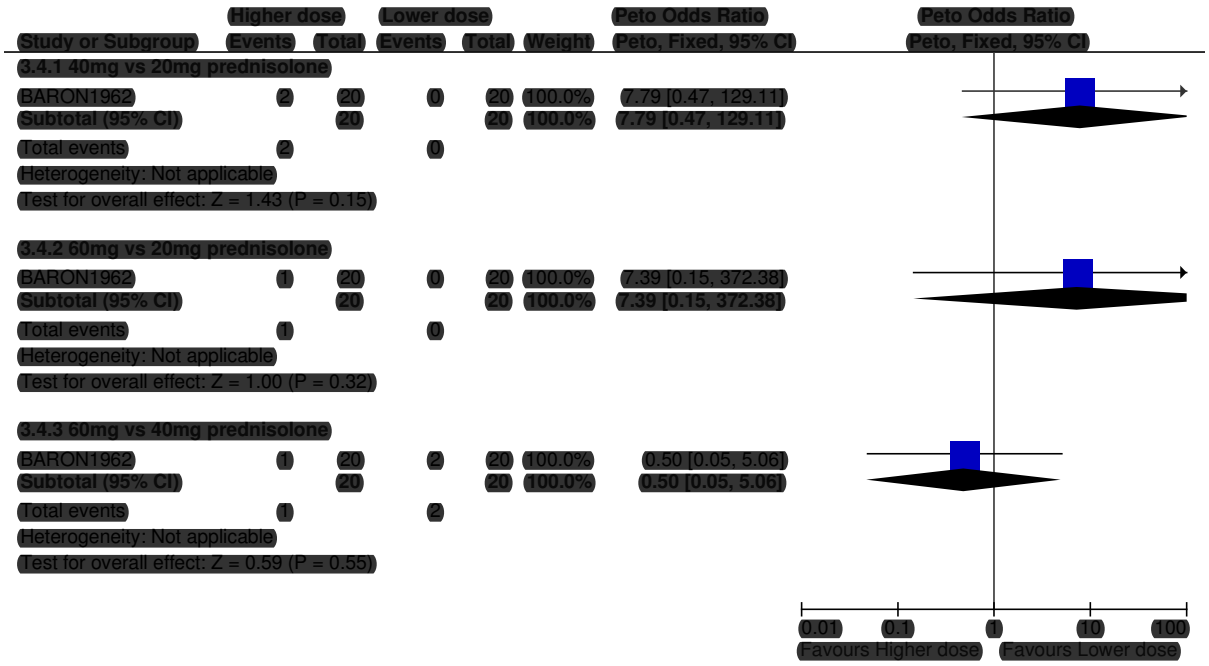


Figure 157: Adverse events

1.1.11.4 Beclomethasone

Figure 158: Clinical improvement

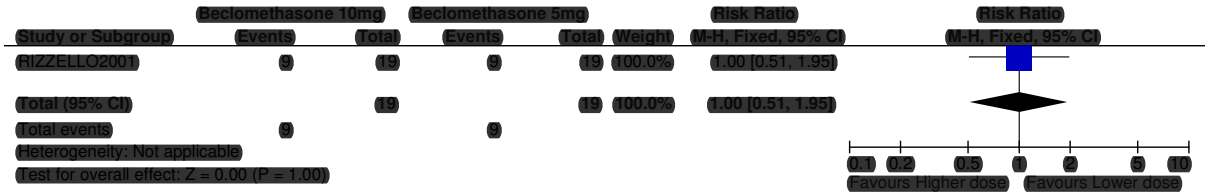
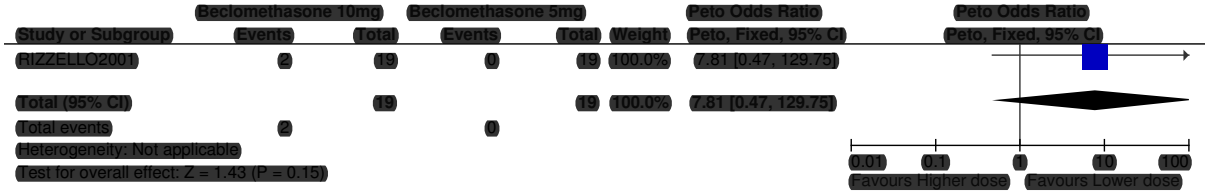


Figure 159: Adverse events



1.1.11.5 Oral corticosteroids regimen comparison

Figure 160: Clinical remission (0≤2 weeks)

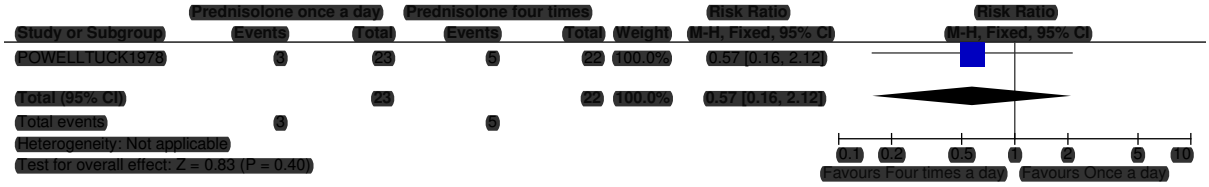
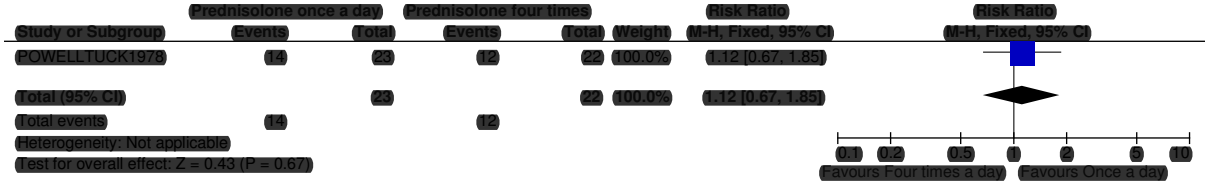


Figure 161: Clinical improvement (0≤2 weeks)



1.1.12 Oral corticosteroids route of administration comparison

1.1.12.1 Oral versus IM corticosteroids

Figure 162: Clinical remission

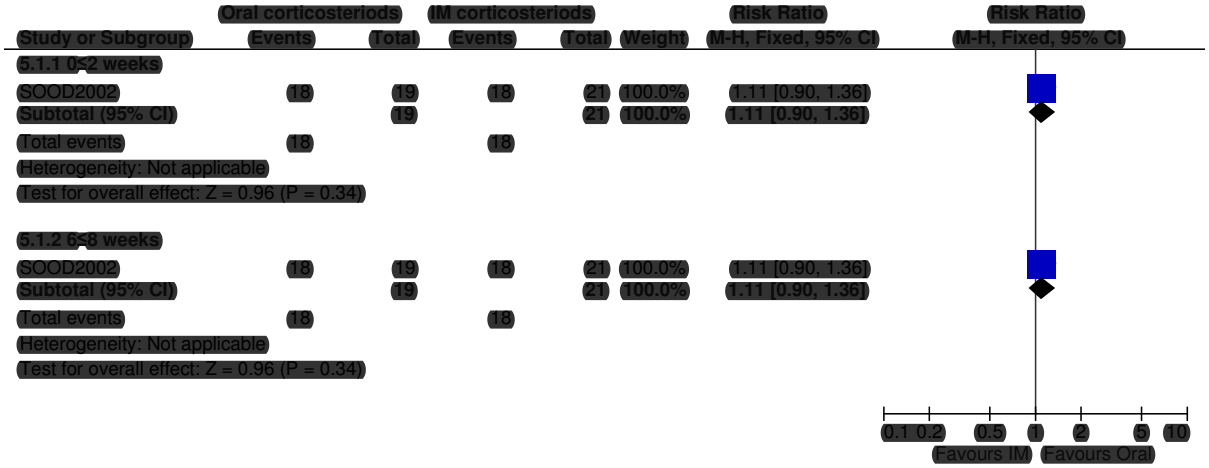
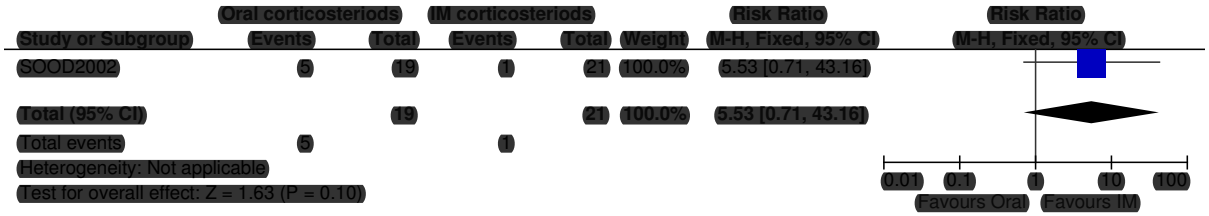


Figure 163: Adverse events



1.1.13 Oral aminosalicylates versus oral corticosteroids

Figure 164: Clinical remission

Figure 165: Clinical improvement

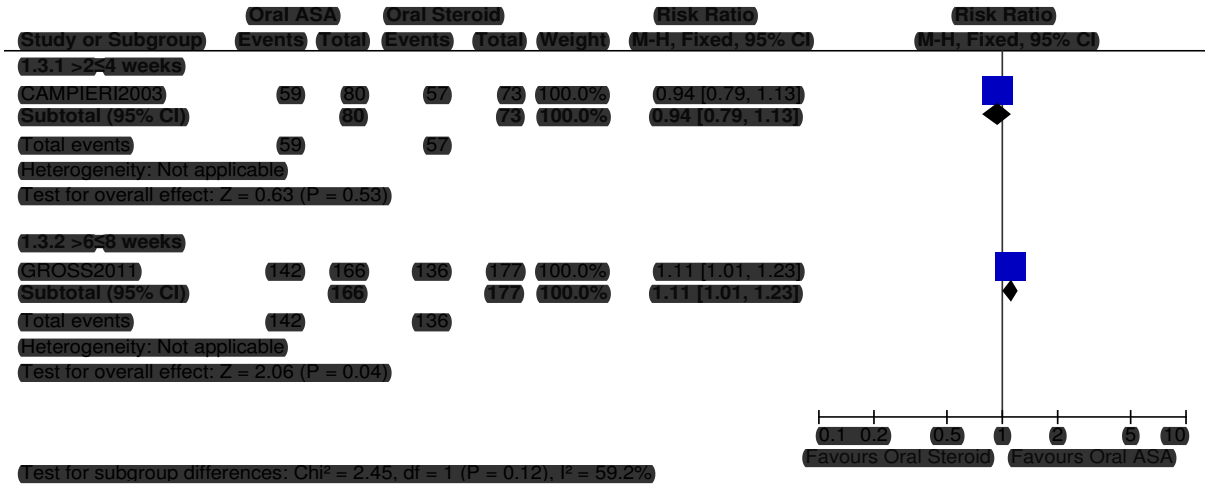


Figure 166: Endoscopic remission

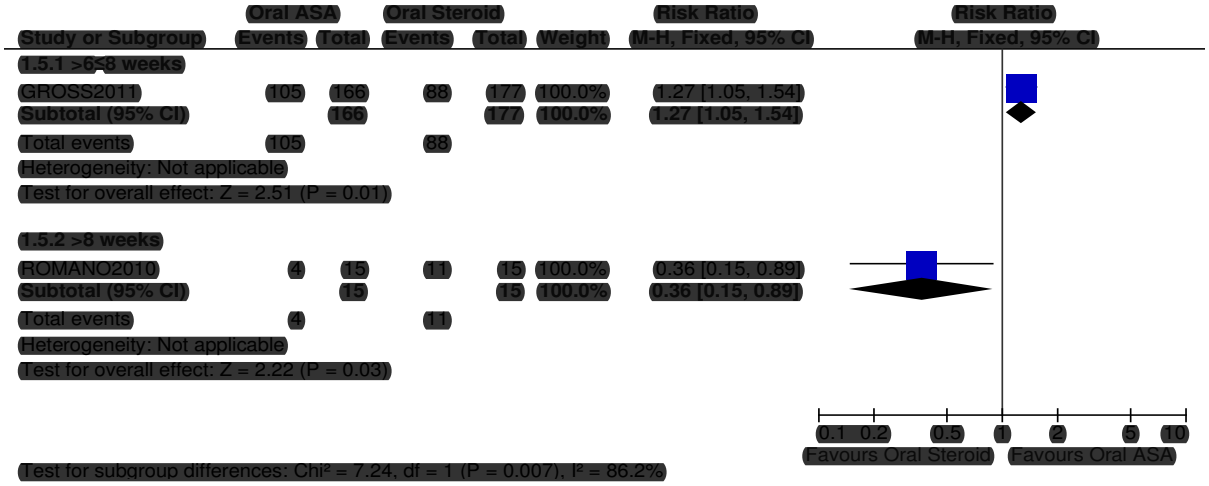


Figure 167: Clinical and endoscopic remission

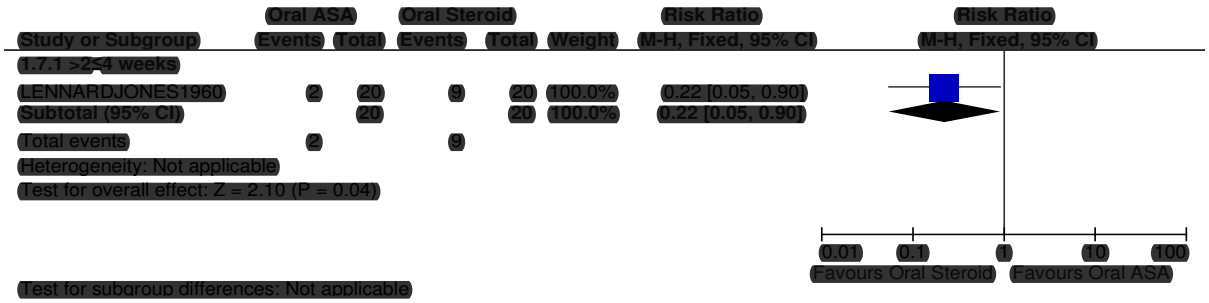


Figure 168: Adverse events

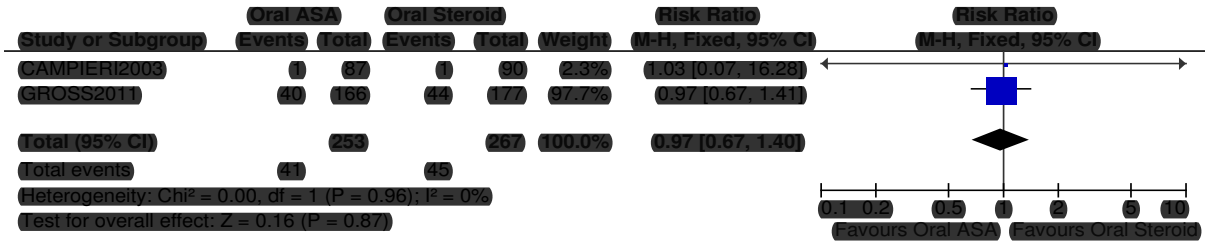
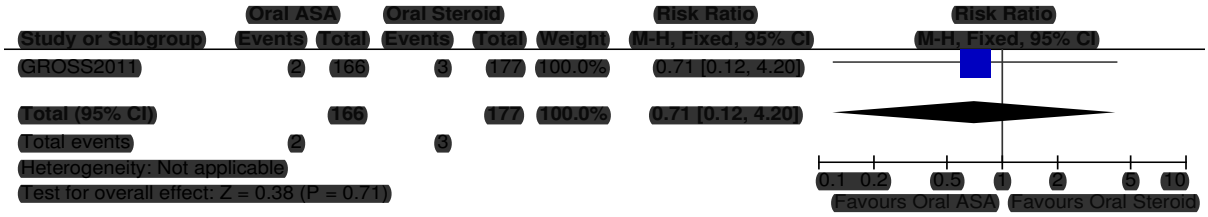


Figure 169: Serious adverse events



1.1.14 Oral aminosalicylates & oral steroids versus oral aminosalicylates & placebo

Figure 170: Clinical remission (>2≤4 weeks)

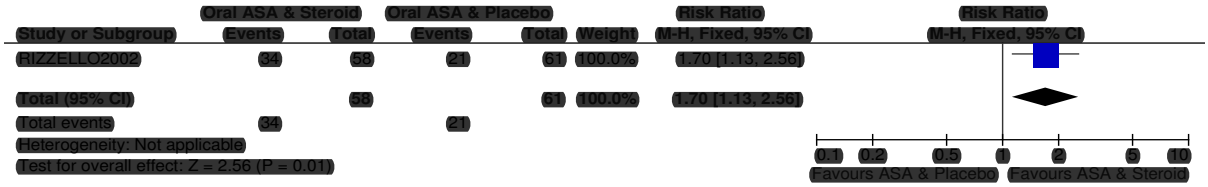


Figure 171: Clinical improvement (>2≤4 weeks) Oral

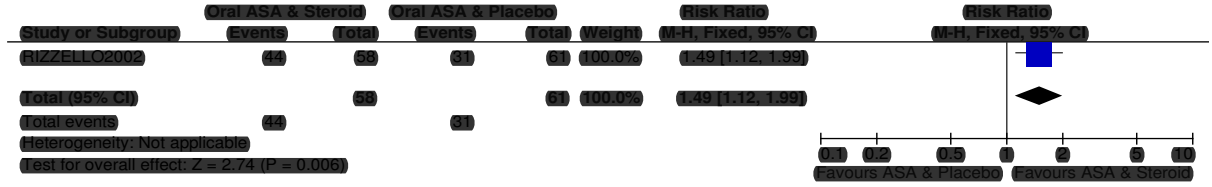


Figure 172: Endoscopic remission (>2≤4 weeks)

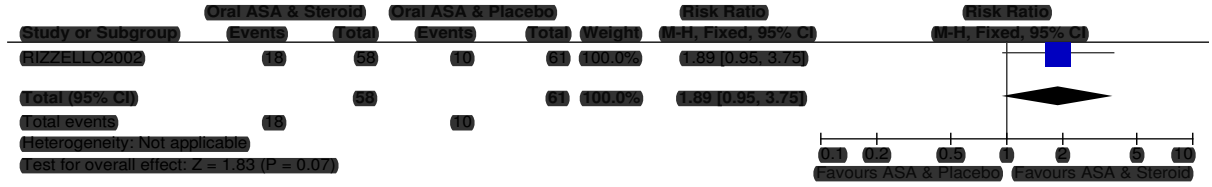
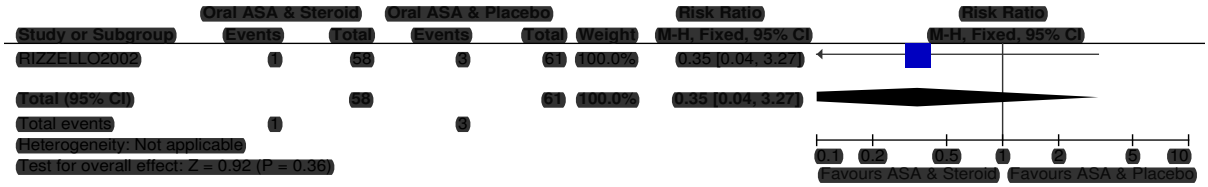


Figure 173: Adverse events



1.1.15 Oral aminosalicylates versus topical aminosalicylates

Figure 174: Clinical remission

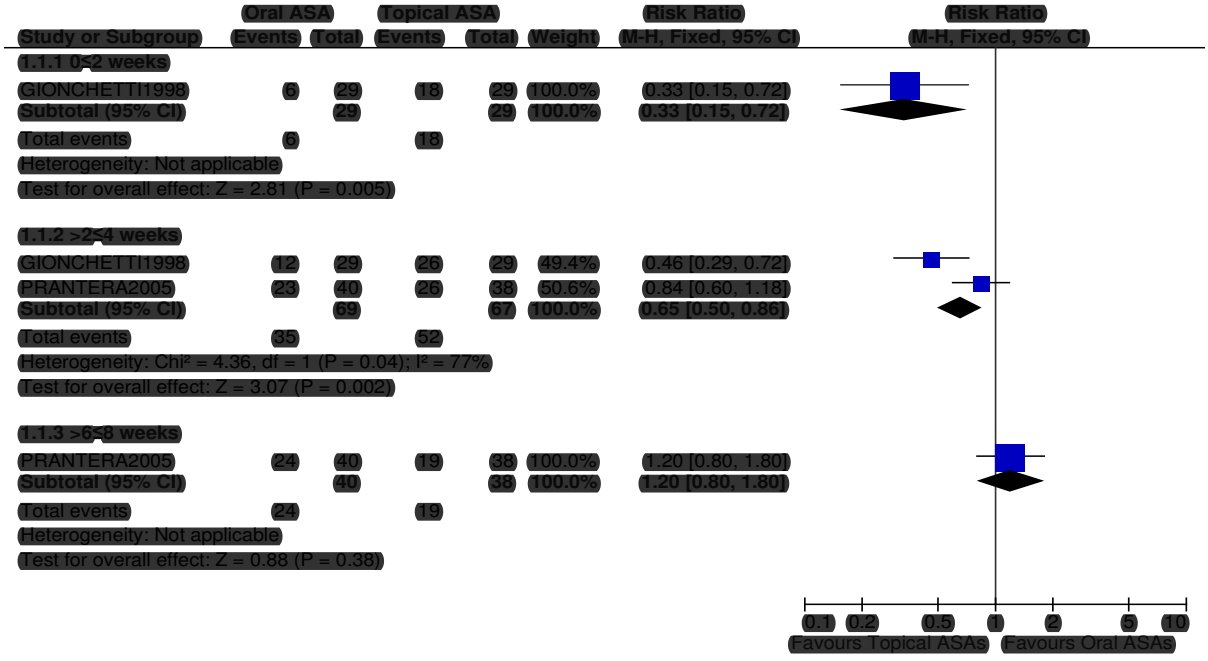


Figure 175: Clinical improvement

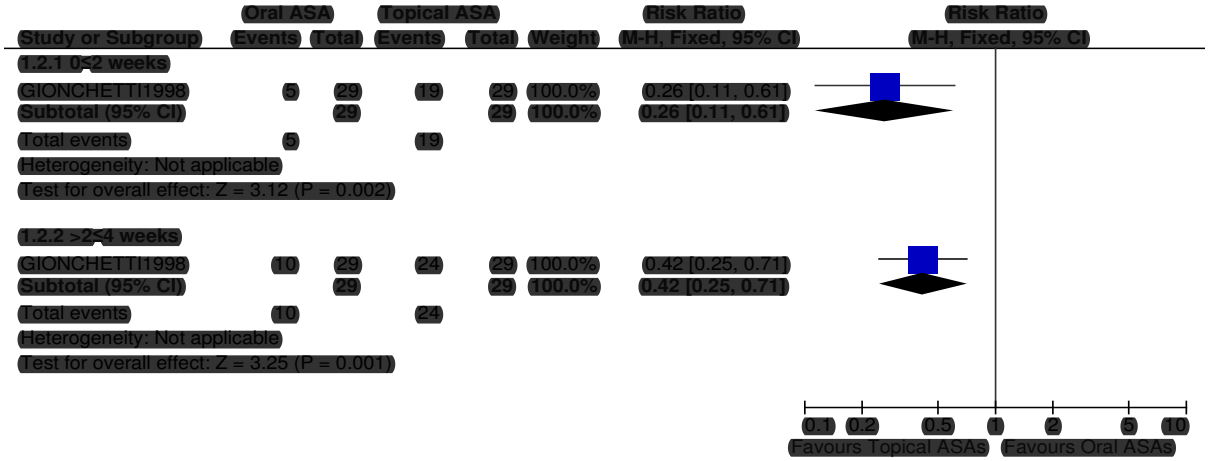


Figure 176: Endoscopic remission

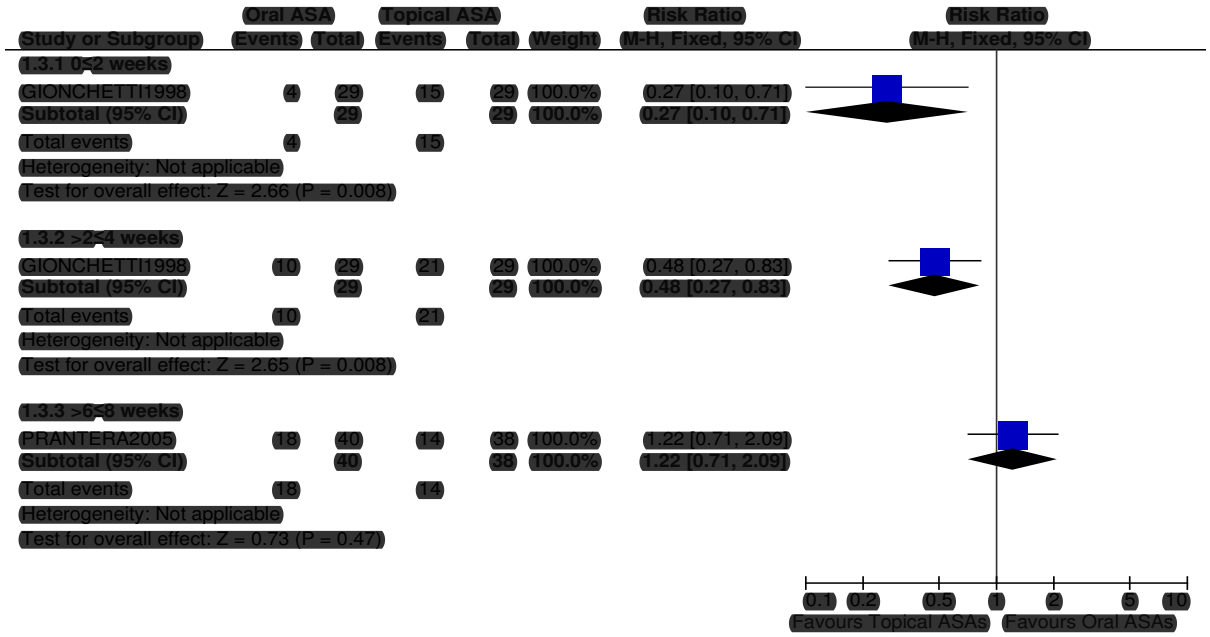
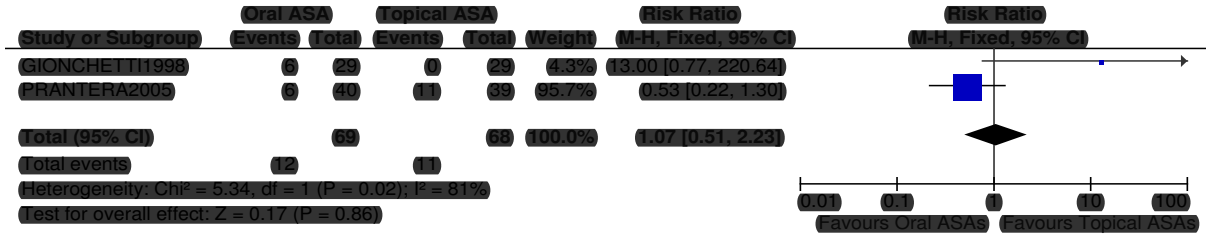


Figure 177: Adverse events



1.1.16 Oral aminosalicylate versus oral & topical aminosalicylate

Figure 178: Clinical remission

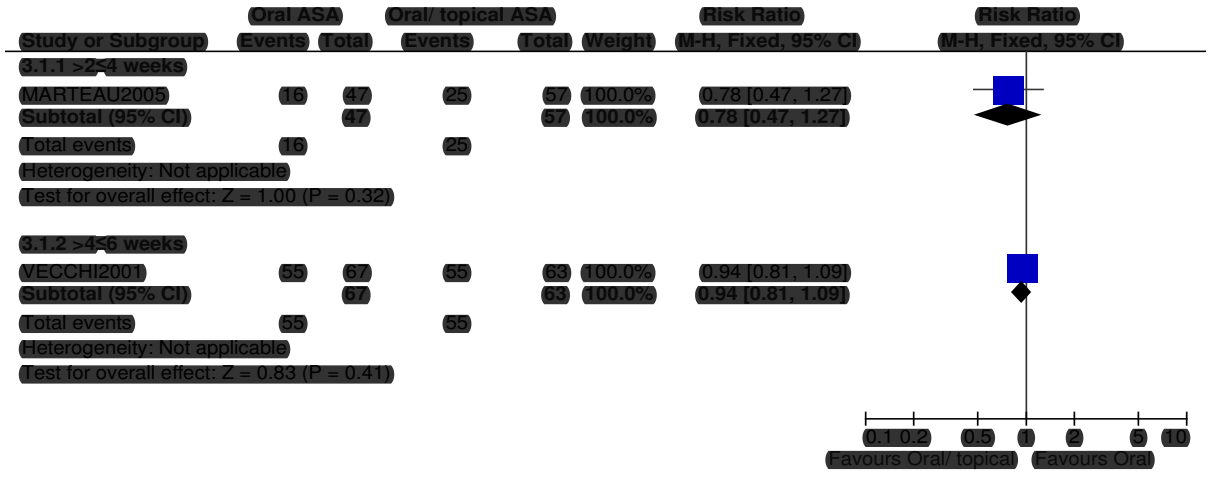


Figure 179: Clinical remission at 8 weeks (4 weeks combination treatment, 4 weeks oral treatment)

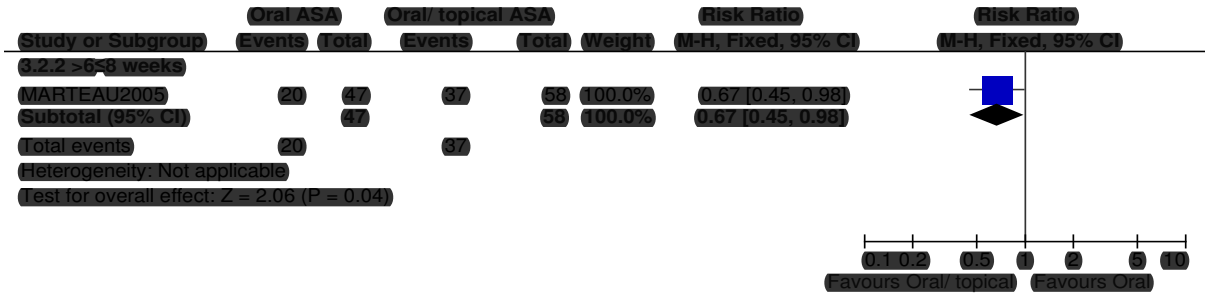


Figure 180: Clinical improvement

Figure 181: Clinical improvement at 8 weeks (4 weeks combination treatment, 4 weeks oral treatment)

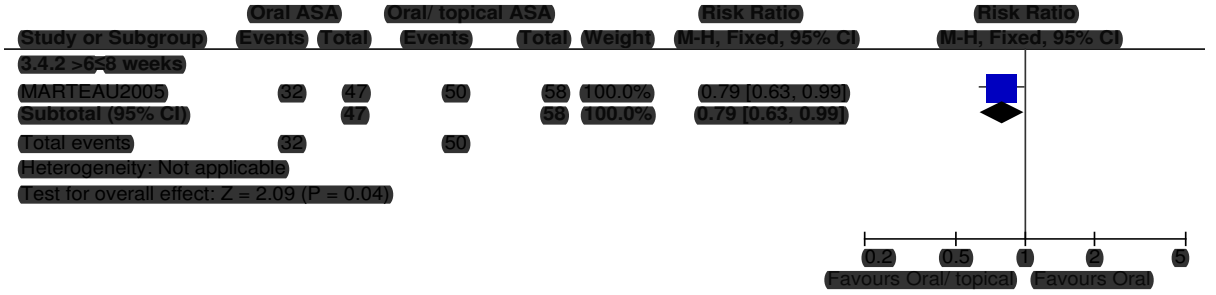


Figure 182: Quality of life

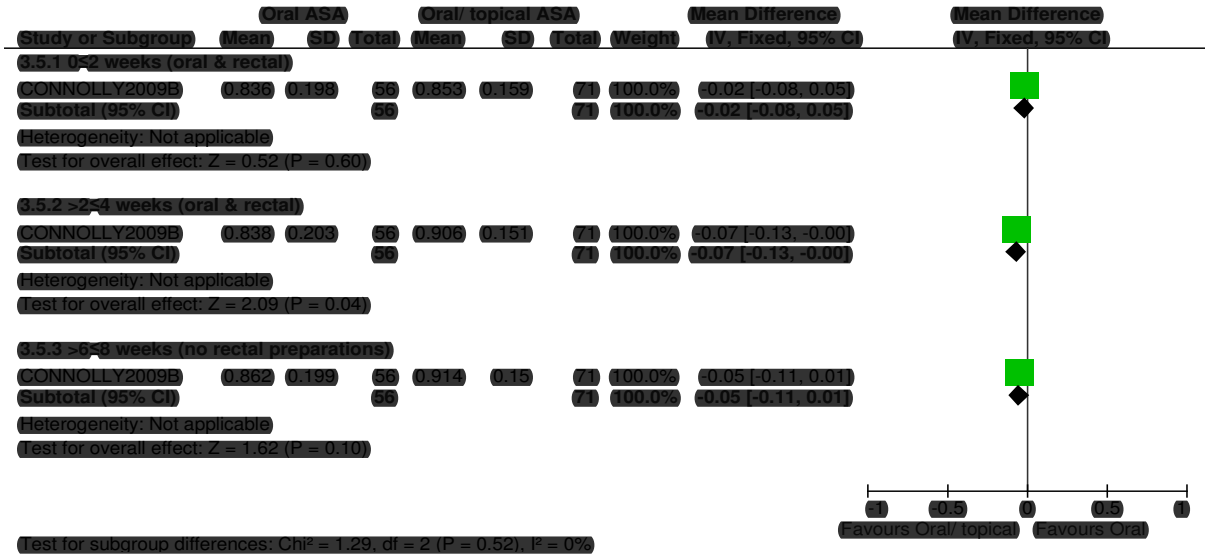


Figure 183: Endoscopic remission

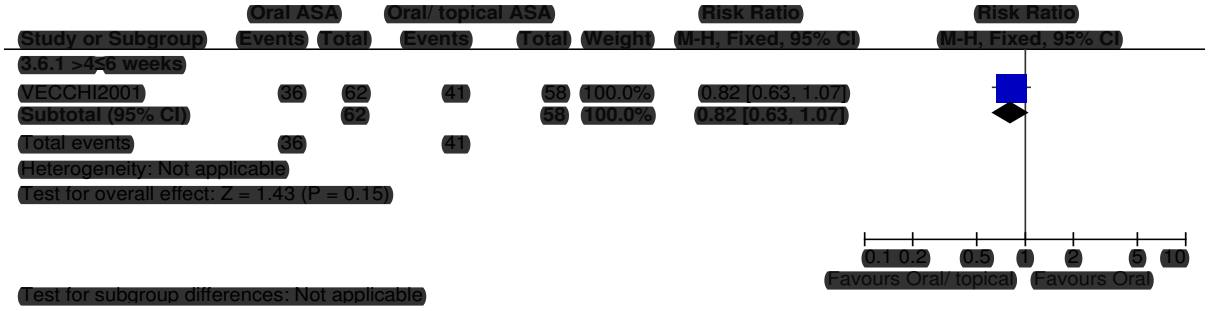


Figure 184: Adverse events (6 weeks of combination treatment)

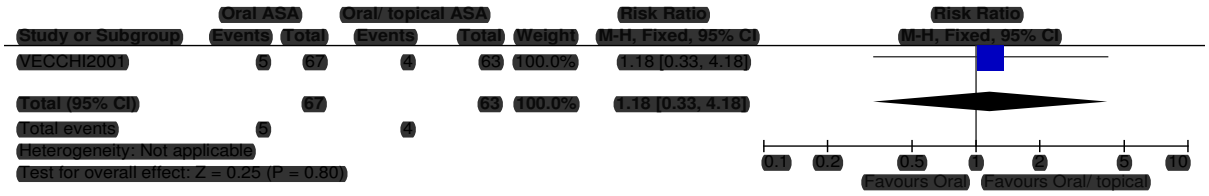


Figure 185: Adverse events at 8 weeks (4 weeks of combination treatment, 4 weeks of oral treatment)

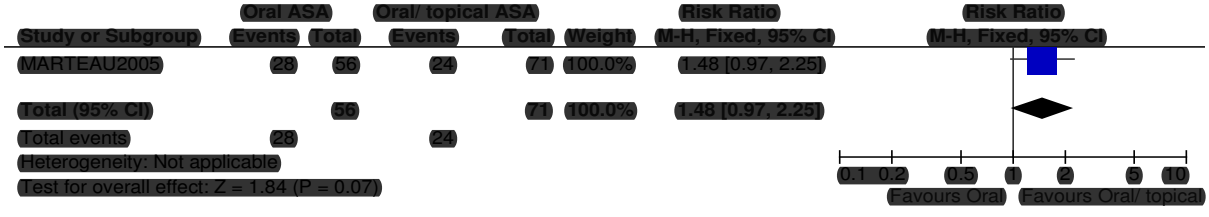
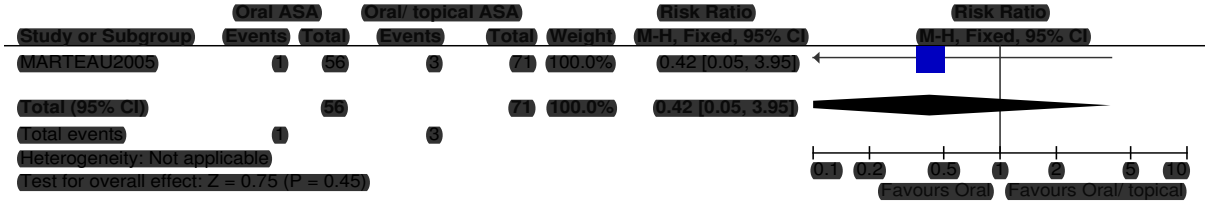
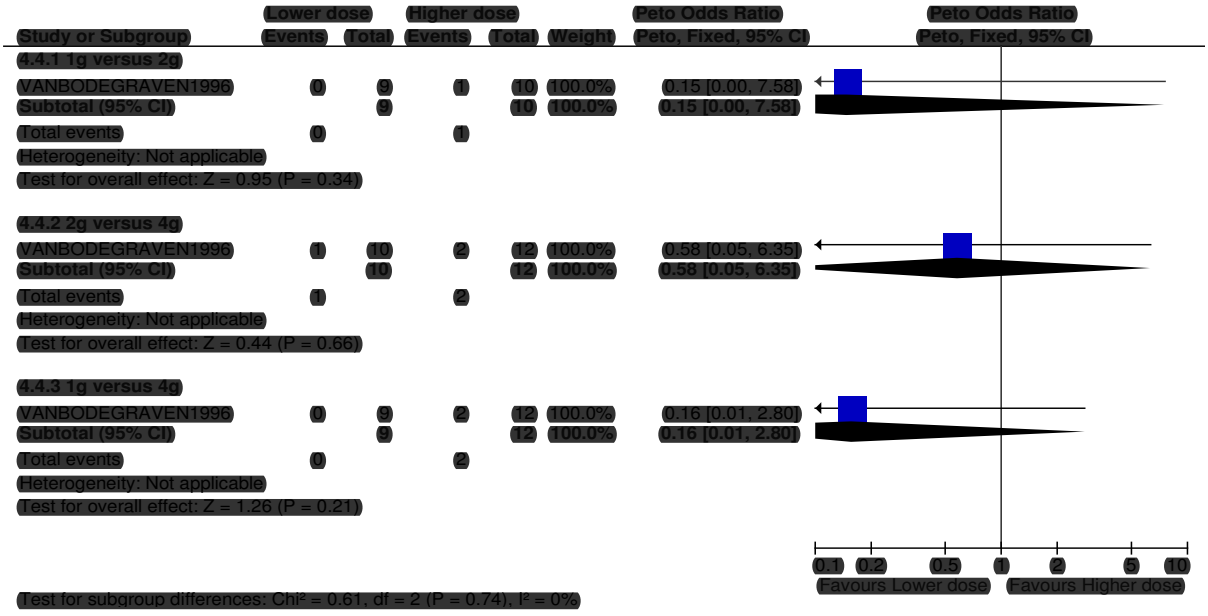


Figure 186: Serious adverse events at 8 weeks (4 weeks of combination treatment, 4 weeks of oral treatment)



1.1.17 Oral & topical aminosalicylate versus oral & topical aminosalicylate (different rectal aminosalicylate doses)

Figure 187: Colectomy at 12 weeks



1.1.18 Immunomodulators

1.1.18.1 Methotrexate versus placebo

Figure 188: Clinical remission

1.1.18.2 Azathioprine versus placebo (in addition to corticosteroids)

Figure 189: Clinical remission

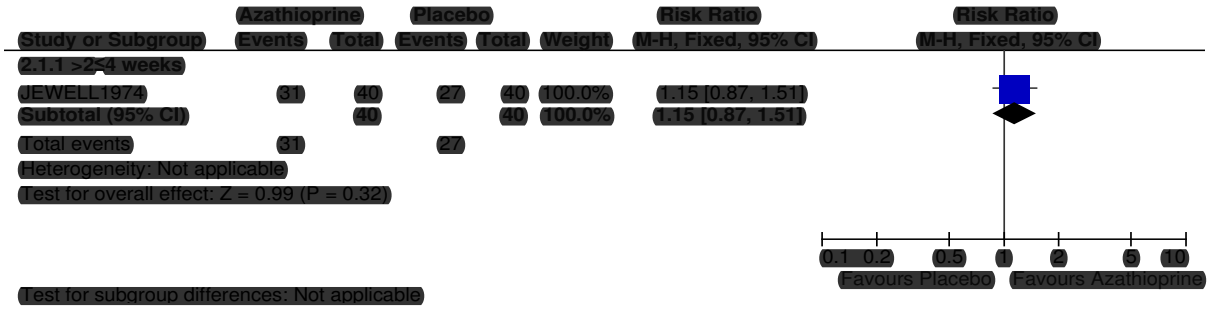
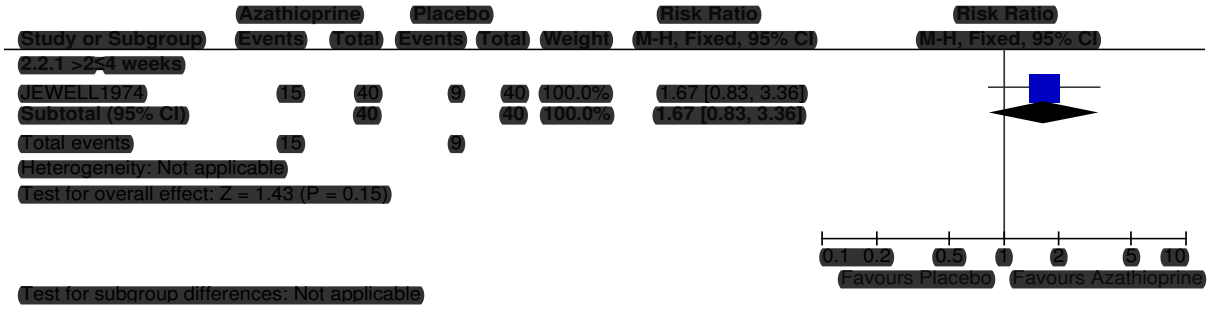


Figure 190: Endoscopic remission



1.1.18.3 Tacrolimus versus placebo

Figure 191: Clinical remission (0≤2 weeks)

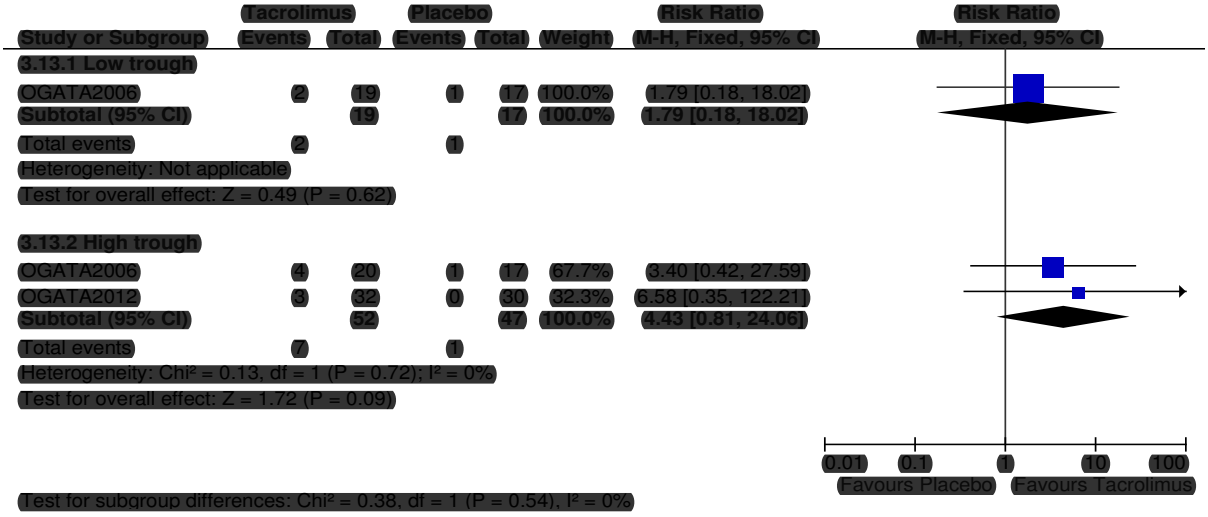


Figure 192: Clinical improvement (0≤2 weeks)

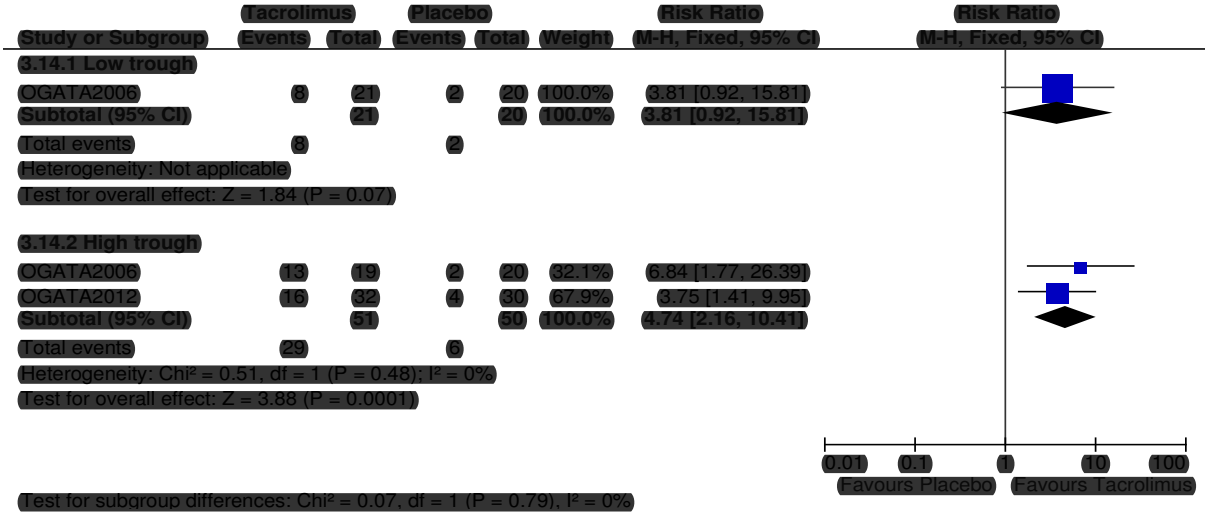


Figure 193: Endoscopic remission(0≤2 weeks)

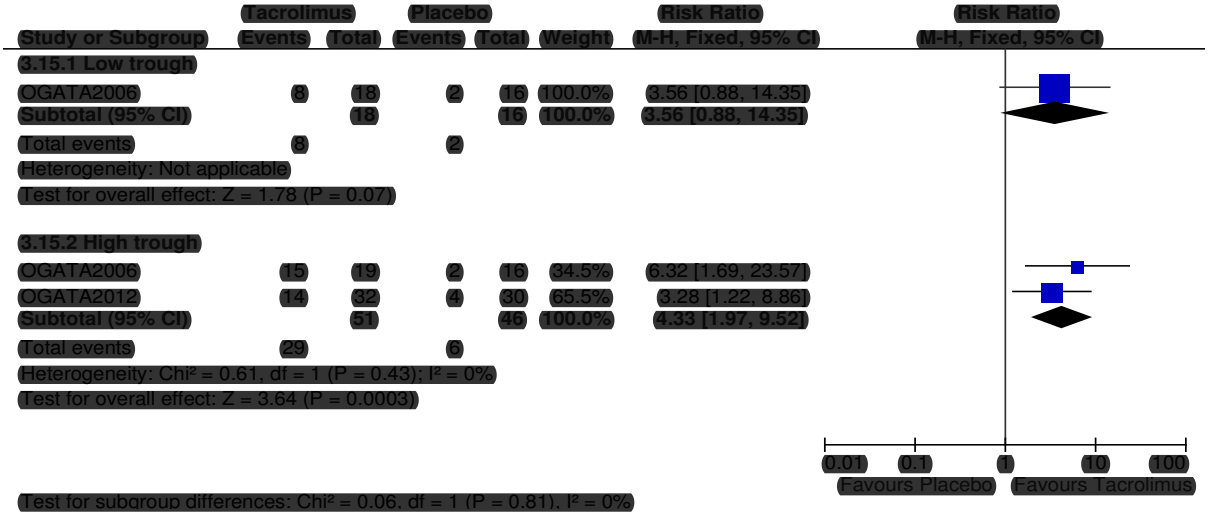


Figure 194: Adverse events

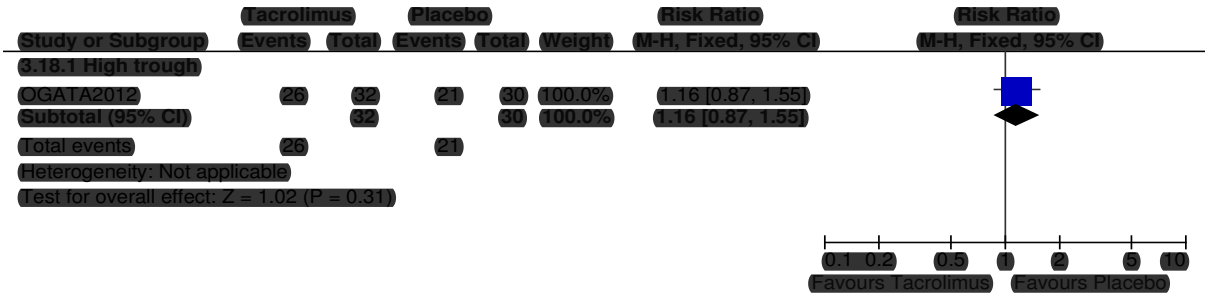
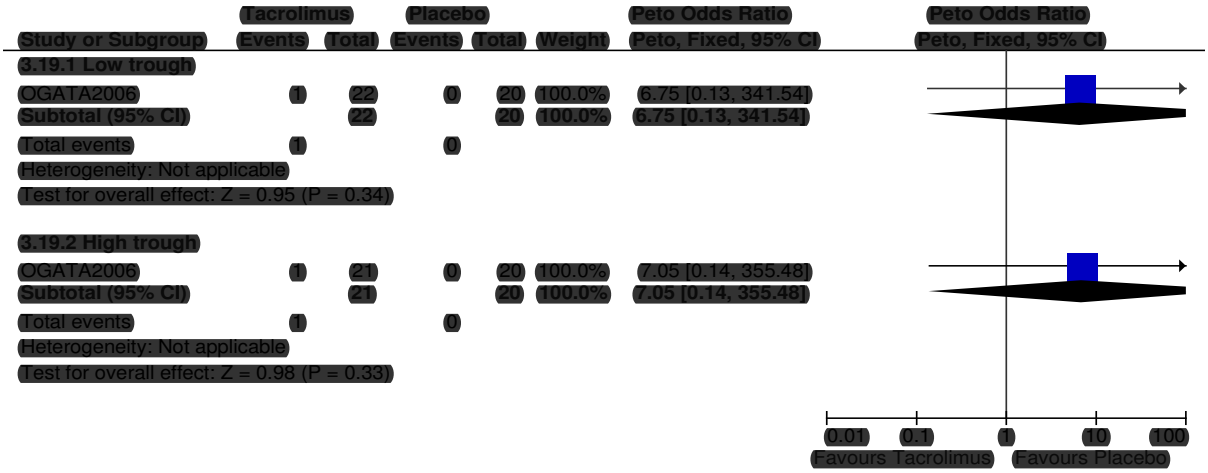


Figure 195: Serious adverse events



1.1.18.4 Tacrolimus dose comparison

Figure 196: Clinical remission (0≤2 weeks)

Figure 197: Clinical improvement (0≤2 weeks)

Figure 198: Endoscopic remission (0≤2 weeks)

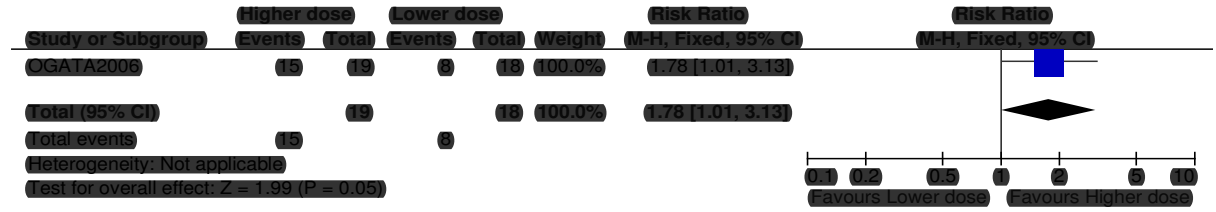
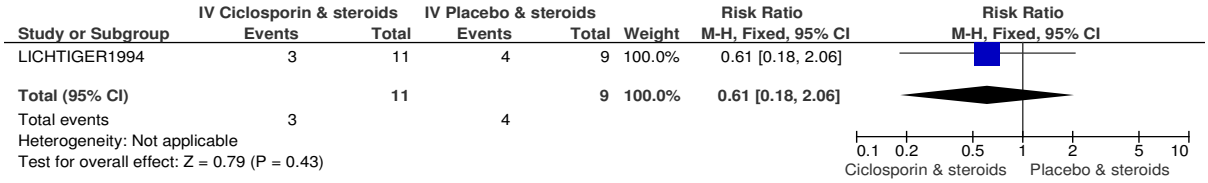


Figure 199: Serious adverse events

1.2 Induction of remission for acute severe ulcerative colitis

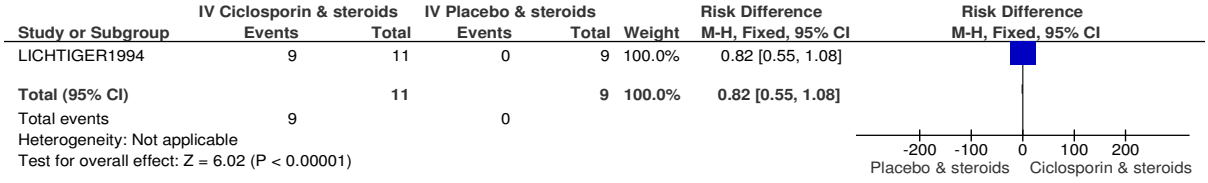
1.2.1.1 IV ciclosporin (4mg/kg) and steroids versus placebo and steroids

Figure 200: Colectomy (0≤2 weeks)



Note: All patients received 100 mg of hydrocortisone IV every 8 hrs and hydrocortisone enemas nightly if the drug could be retained.

Figure 201: Clinical improvement (0≤2 weeks)



1.2.1.2 IV ciclosporin (4mg/kg/day) versus IV steroids (40mg/day)

Figure 202: Colectomy (0≤2 weeks)

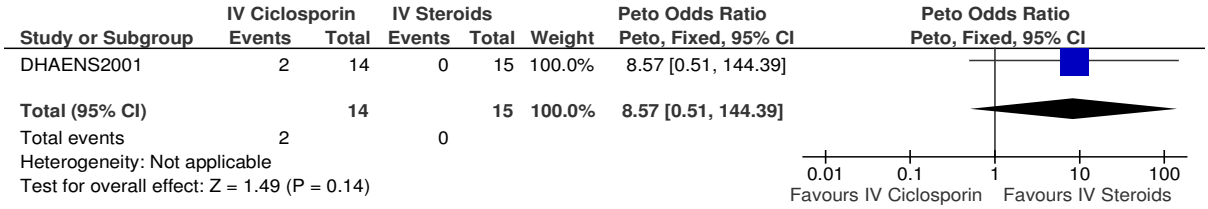
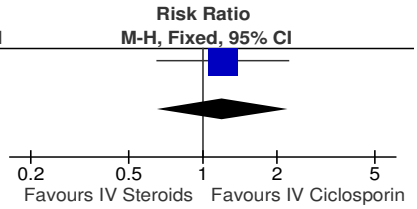


Figure 203: Clinical improvement (0≤2 weeks) – Day 7/8

Study or Subgroup	IV Ciclosporin Events	Total	IV Steroids Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DHAENS2001	9	14	8	15	100.0%	1.21 [0.65, 2.23]
Total (95% CI)		**14**		**15**	**100.0%**	**1.21 [0.65, 2.23]**
Total events	9		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

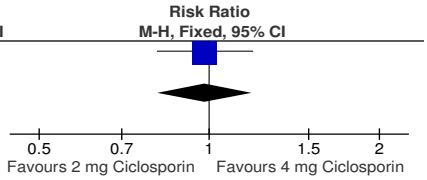


1.2.1.3 Ciclosporin dose comparison: 4 mg/kg versus 2 mg/kg

Figure 204: Clinical improvement (0≤2 weeks)

Study or Subgroup	4 mg IV Ciclosporin Events	Total	2 mg IV Ciclosporin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VAN2003	32	38	30	35	100.0%	0.98 [0.81, 1.19]
Total (95% CI)		**38**		**35**	**100.0%**	**0.98 [0.81, 1.19]**
Total events	32		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)



1.2.1.4 Corticosteroid preparation comparison: IV (infusion) versus IV (bolus)

Figure 205: Colectomy

Study or Subgroup	Infusion Events	Total	Bolus Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 >2≤4 weeks						
BOSSA2007	5	34	5	32	100.0%	0.94 [0.30, 2.95]
Subtotal (95% CI)		**34**		**32**	**100.0%**	**0.94 [0.30, 2.95]**
Total events	5		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

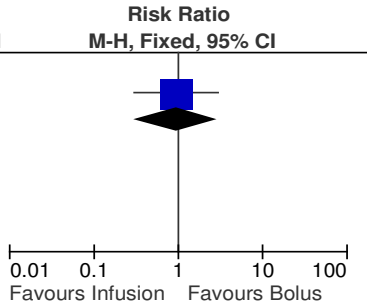


Figure 206: Clinical remission

Study or Subgroup	Infusion Events	Total	Bolus Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 0≤2 weeks						
BOSSA2007	17	34	16	32	100.0%	1.00 [0.62, 1.62]
Subtotal (95% CI)		**34**		**32**	**100.0%**	**1.00 [0.62, 1.62]**
Total events	17		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Test for subgroup differences: Not applicable

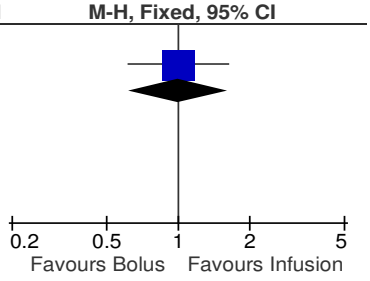
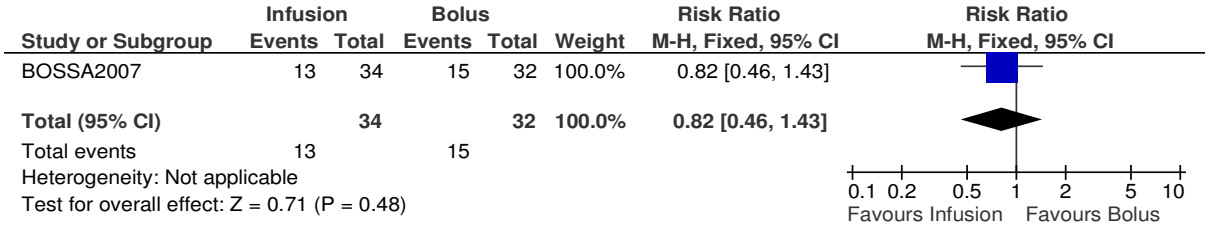


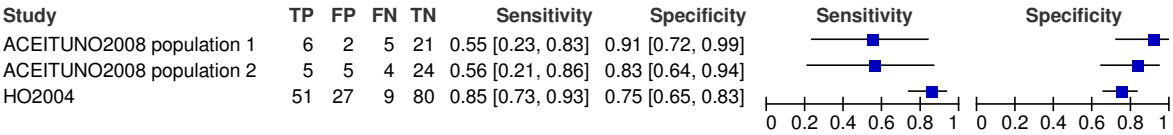
Figure 207: Adverse events



1.3 Likelihood of surgery – Forest plots and Receiver Operator Characteristic (ROC) curves

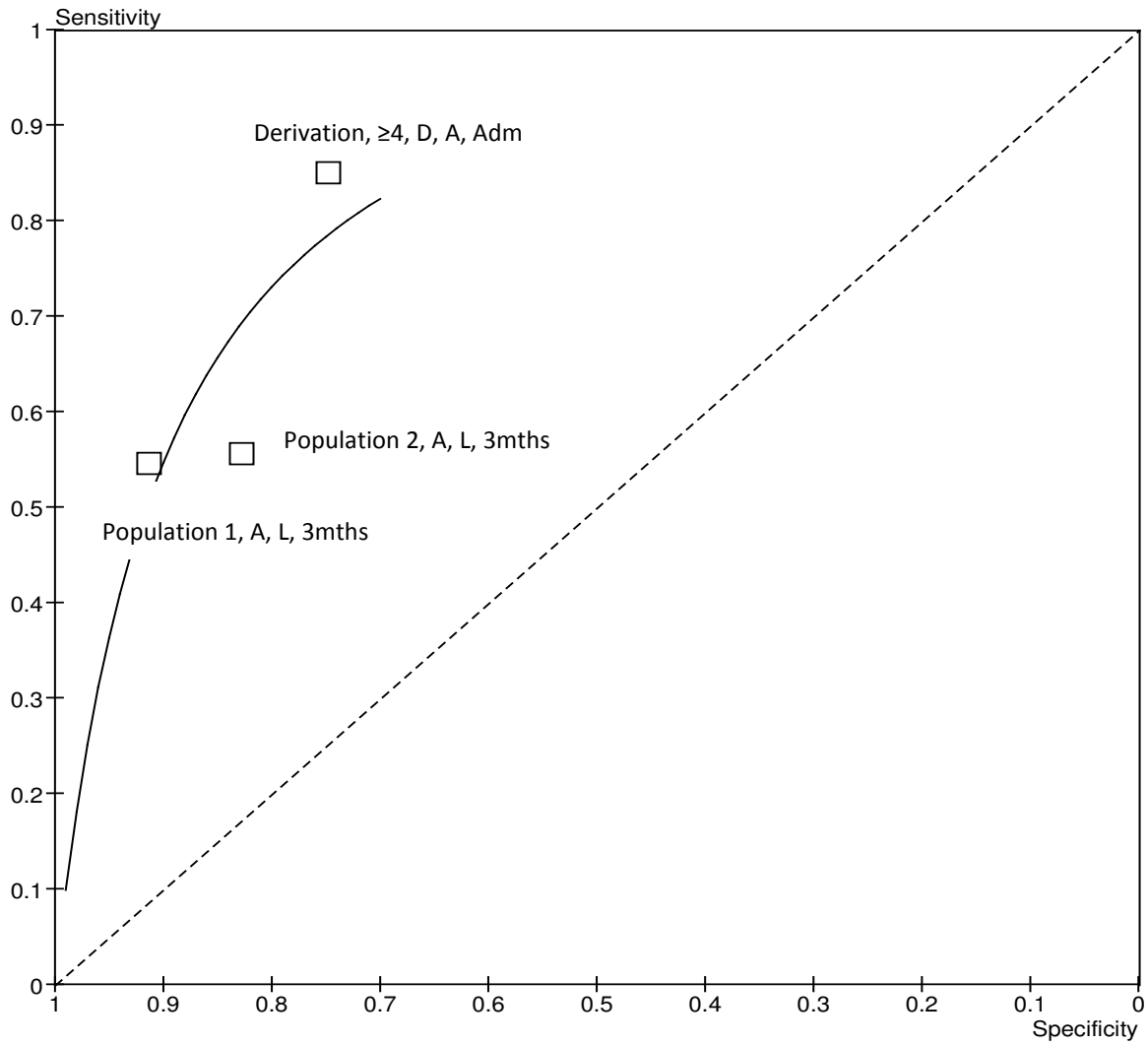
1.3.1 Ho index

Figure 208: Ho Index on Day 3



Source/Note: ACEITUNO2008 cut off ≥5 colectomy in first 3 months, HO2004 cut off≥4 colectomy during hospital admission

Figure 209: ROC curve – Ho index on Day 3



A= adult population

D= derivation study

L= low quality

Adm = colectomy during hospital admission

3mths= colectomy within 3months of admission

1.3.2 Lindgren Index

Figure 210: Lindgren index (different time points and cut offs)

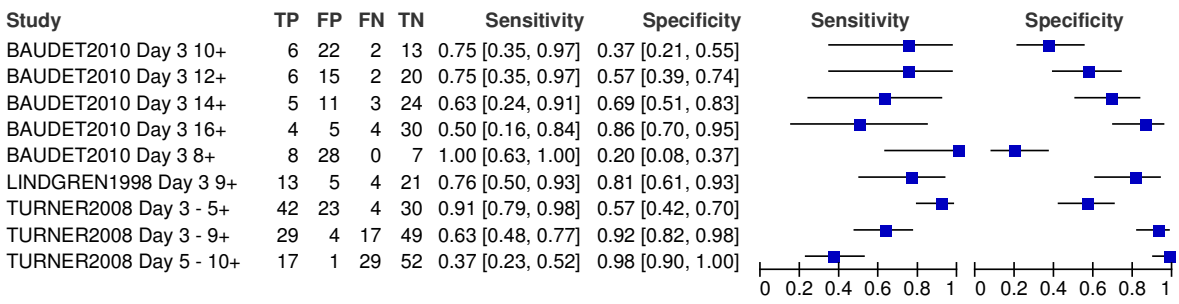
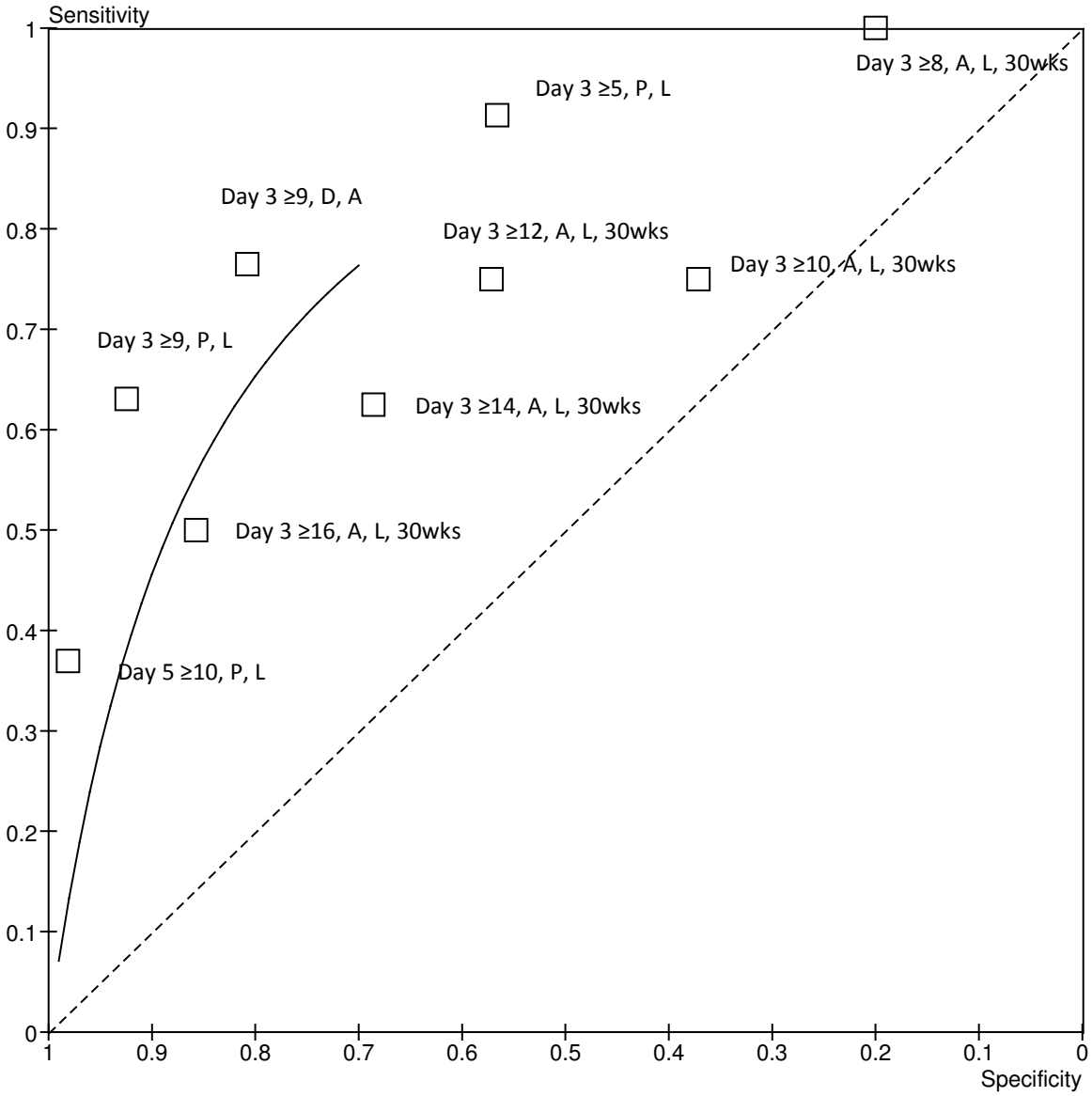


Figure 211: ROC curve for the Lindgren Index (different time points and cut offs)



A= adult population

D=derivation study, 30 days colectomy

30wks= 30wks colectomy

P= paediatric population, within admission colectomy

L= low quality

The ≥ figures indicate the cut offs used.

Note: The adult population study were patients who were on infliximab

1.3.3 Seo Index

Figure 212: Seo index (different time points and cut offs)

Study	TP	FP	FN	TN	Sensitivity	Specificity
SEO2002 1wk 180	33	31	2	57	0.94 [0.81, 0.99]	0.65 [0.54, 0.75]
SEO2002 2wks 180	30	13	4	75	0.88 [0.73, 0.97]	0.85 [0.76, 0.92]
SEO2002 2wks 190	28	10	6	78	0.82 [0.65, 0.93]	0.89 [0.80, 0.94]
SEO2002 2wks 200	24	5	10	83	0.71 [0.53, 0.85]	0.94 [0.87, 0.98]
SEO2002 2wks 210	17	4	17	84	0.50 [0.32, 0.68]	0.95 [0.89, 0.99]
SEO2002 pretx 210	23	28	16	60	0.59 [0.42, 0.74]	0.68 [0.57, 0.78]
TURNER2008 Day 3 - 196+	42	30	4	23	0.91 [0.79, 0.98]	0.43 [0.30, 0.58]
TURNER2008 Day 5 - 241+	12	4	34	49	0.26 [0.14, 0.41]	0.92 [0.82, 0.98]

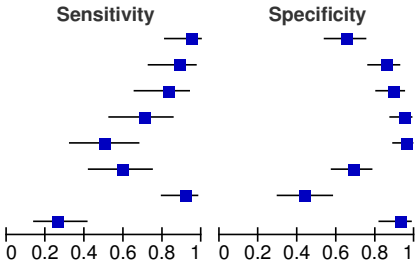
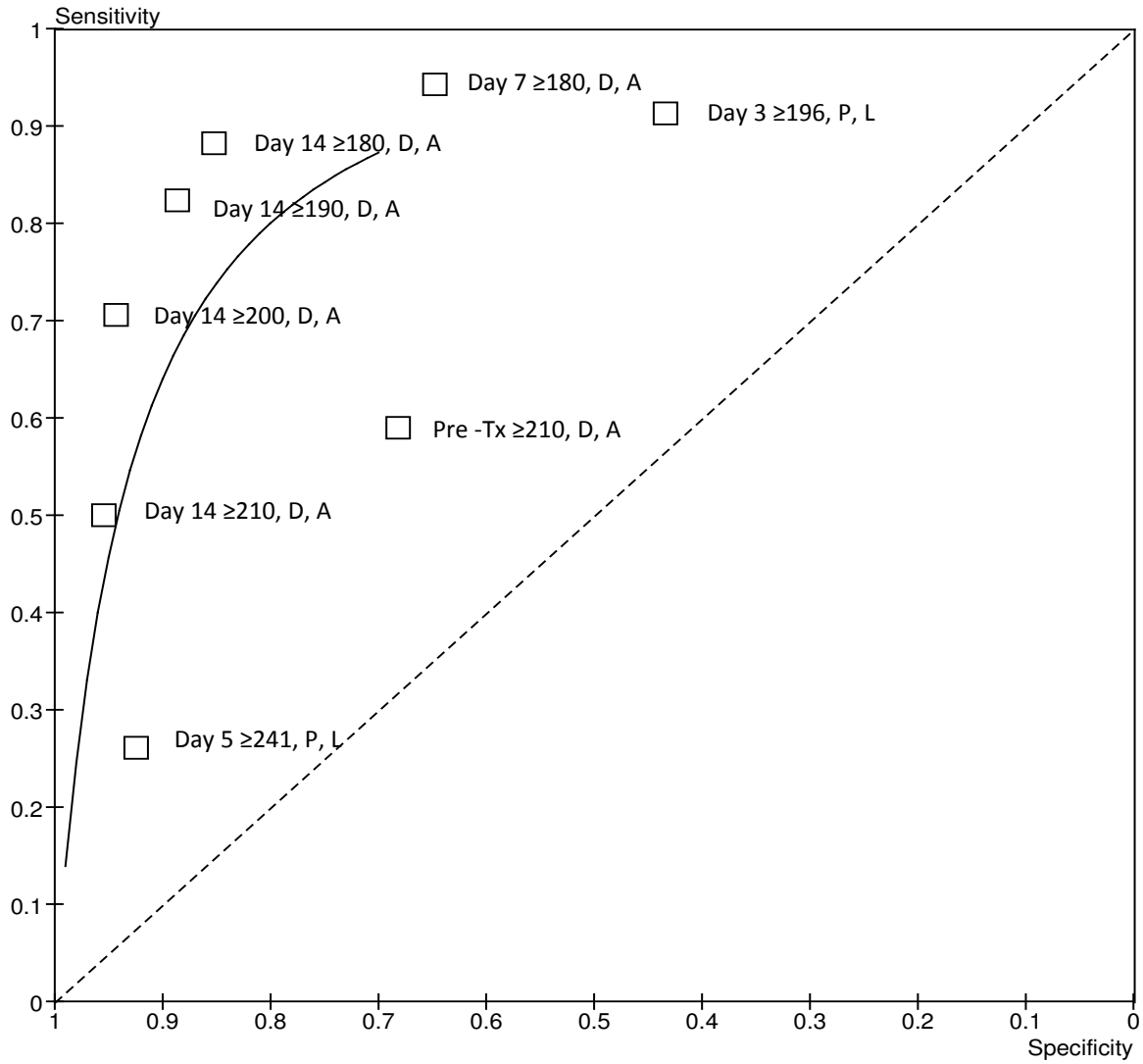


Figure 213: ROC curve for Seo Index (different time points and cut offs)



A= adult population

D=derivation study

P= paediatric population

L= low quality

The ≥ figures indicate the cut offs used.

1.3.4 Travis Index

Figure 214: Travis index (different time points)

Study	TP	FP	FN	TN	Sensitivity	Specificity
TRAVIS1996 Day 3 episode	12	4	3	32	0.80 [0.52, 0.96]	0.89 [0.74, 0.97]
TRAVIS1996 Day 3 patient	11	4	3	31	0.79 [0.49, 0.95]	0.89 [0.73, 0.97]
TURNER2008 Day 3	17	0	29	53	0.37 [0.23, 0.52]	1.00 [0.93, 1.00]
TURNER2008 Day 5	10	0	36	53	0.22 [0.11, 0.36]	1.00 [0.93, 1.00]

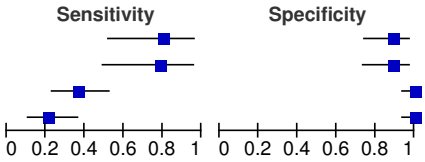
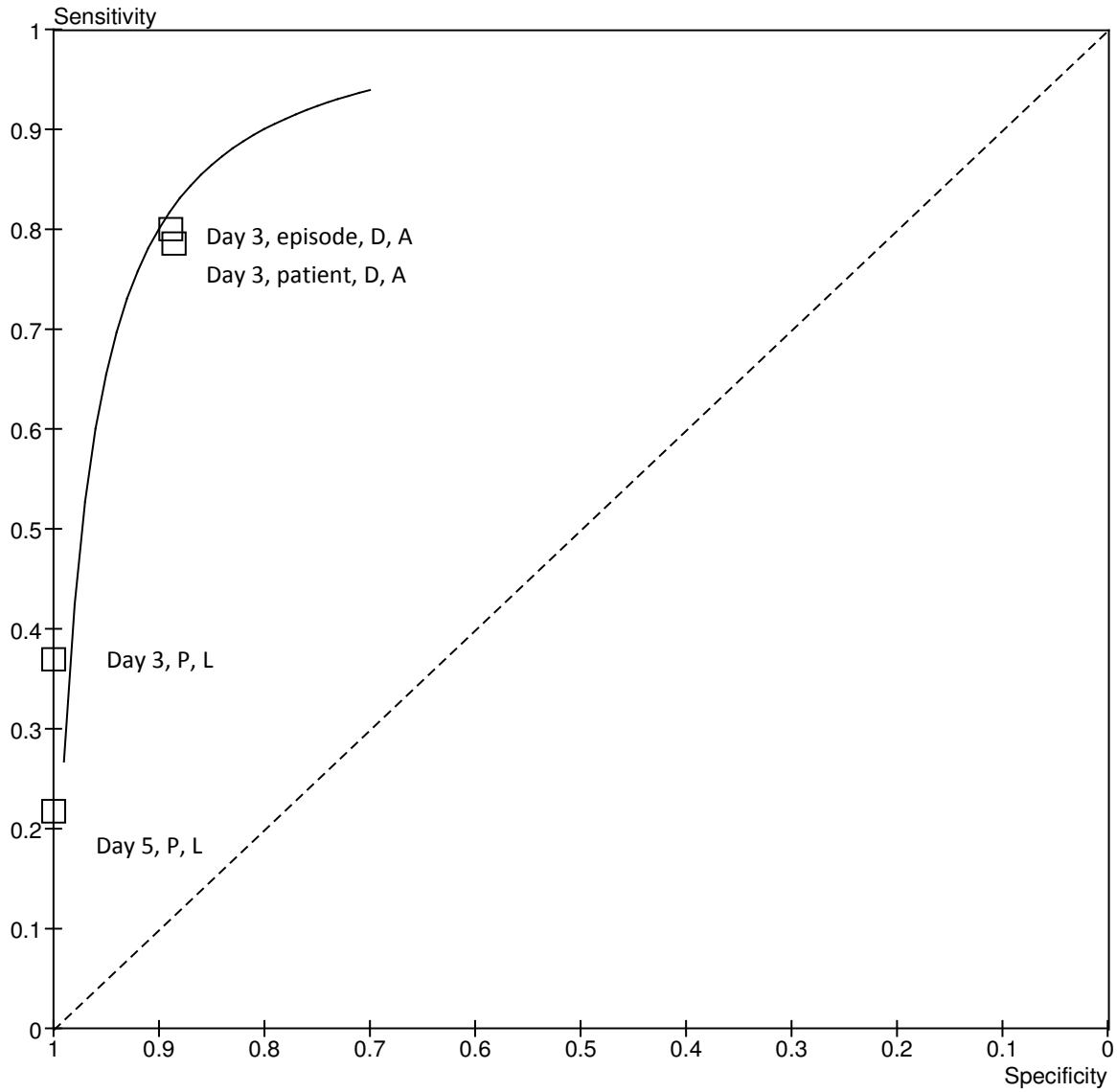


Figure 215: ROC curve for the Travis index (different time points)



Episode/ patient – denominator used for analysis

A= adult population

D=derivation study

P= paediatric population

L=low quality

1.4 Maintenance of remission

1.4.1 Topical aminosalicylates

1.4.1.1 Topical aminosalicylates versus placebo (continuous)

Figure 216: Relapse (HR)

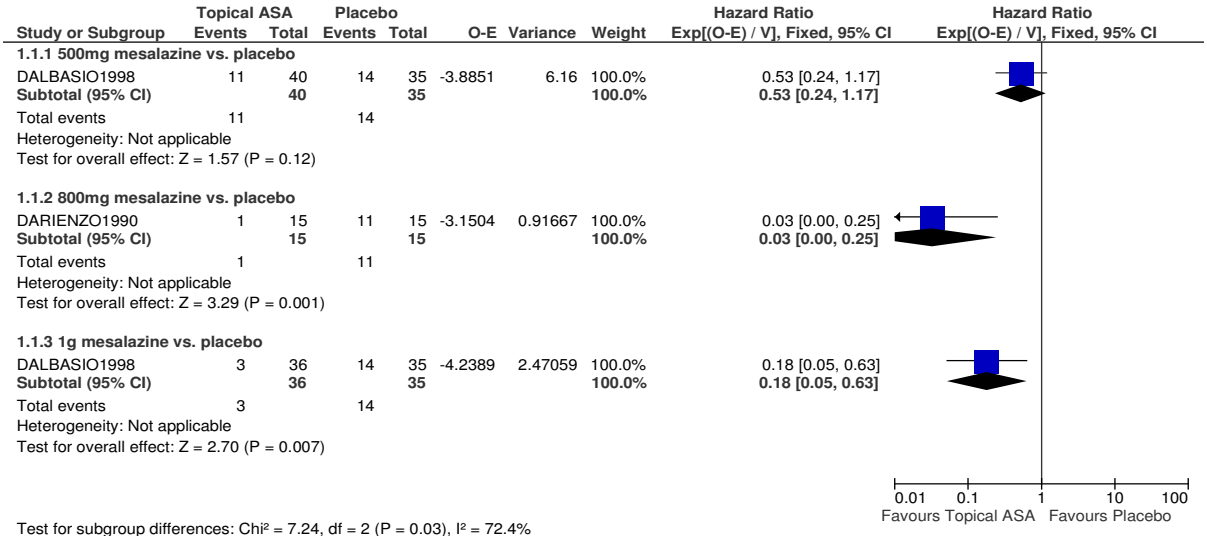
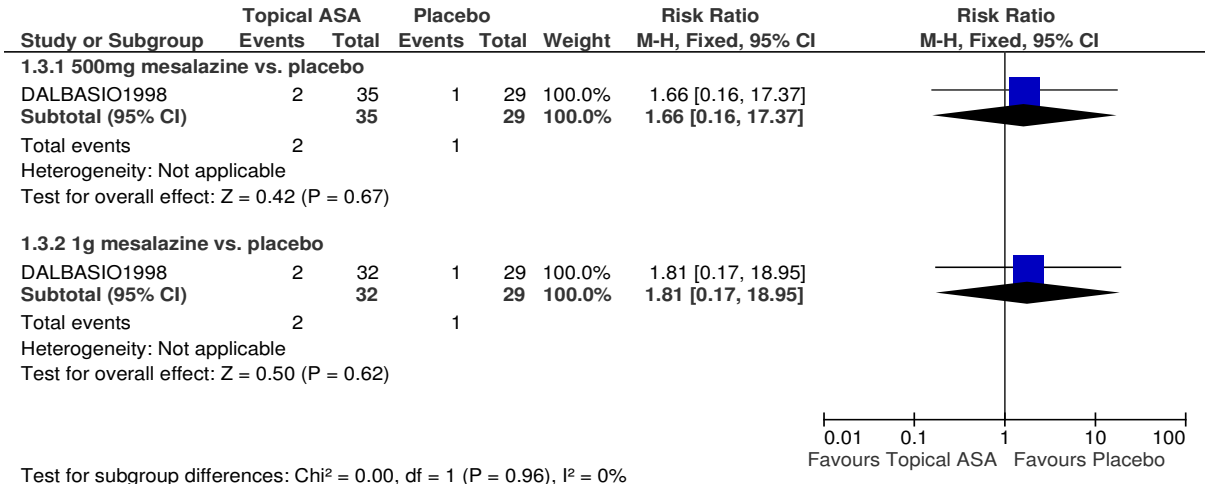


Figure 217: Adverse events



1.4.1.2 Topical aminosalicylates versus placebo (intermittent)

Figure 218: Relapse at 1 year (RR)

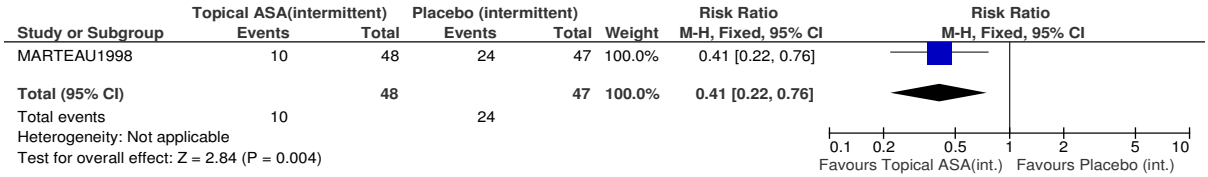
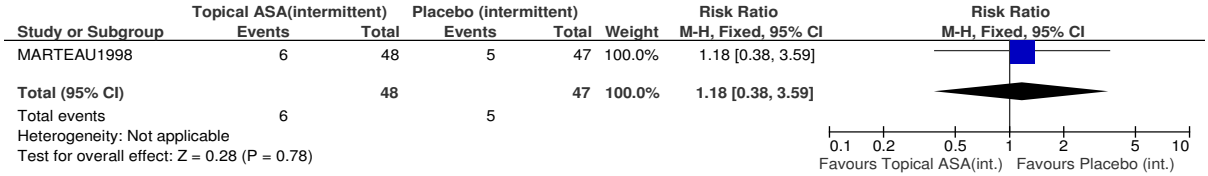


Figure 219: Adverse events



1.4.1.3 Topical aminosalicylates dose comparison

Figure 220: Relapse (HR)

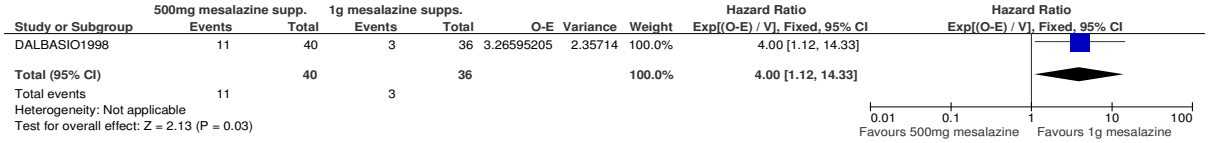
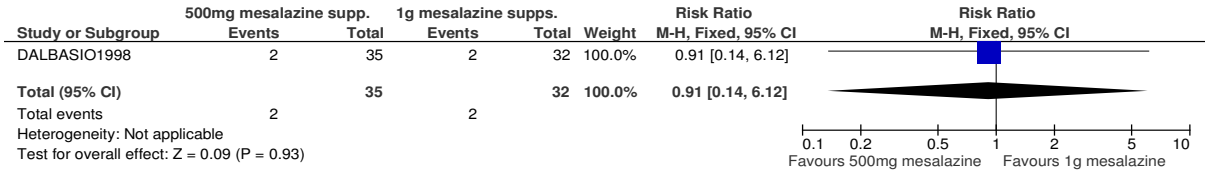


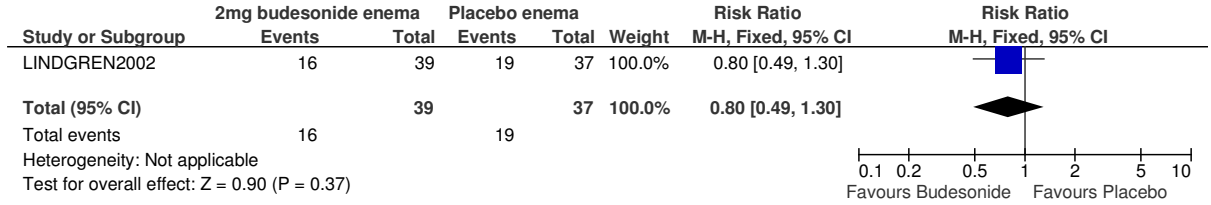
Figure 221: Adverse events



1.4.2 Topical corticosteroids

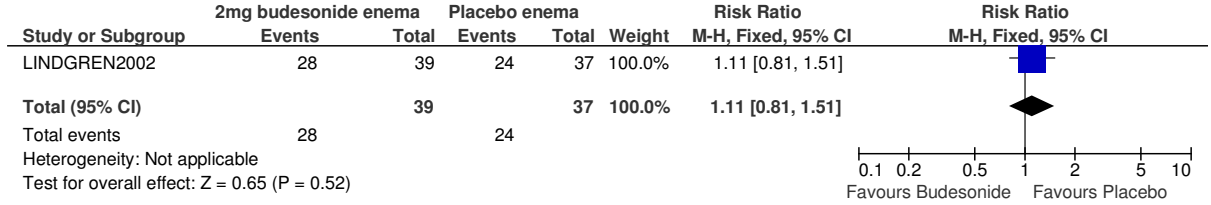
1.4.2.1 Topical corticosteroids versus placebo (intermittent)

Figure 222: Relapse at 26 weeks



Note: 2mg Budesonide liquid enema twice a week versus placebo enema twice a week

Figure 223: Adverse events



1.4.3 Oral aminosalicylates

1.4.3.1 Oral aminosalicylates versus placebo

Figure 224: Relapse (HR)

Study or Subgroup	Oral ASA Events	Oral ASA Total	Placebo Events	Placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ARDIZZONE1999C 12-24 mths	6	26	17	35	-5.7574	5.62483	10.6%	0.36 [0.16, 0.82]
ARDIZZONE1999C 2 years +	5	28	6	23	-1.3866	2.72357	5.1%	0.60 [0.18, 1.97]
HANAUER1996A 1.6g	18	58	33	63	-8.6777	11.6471	21.8%	0.47 [0.27, 0.84]
MINER1995	35	103	56	99	-9.8949	21.5385	40.4%	0.63 [0.41, 0.96]
WRIGHT1993	19	49	31	52	-7.75	11.78	22.1%	0.52 [0.29, 0.92]
Total (95% CI)		**264**		**272**			**100.0%**	**0.53 [0.41, 0.70]**
Total events	83		143					

Heterogeneity: Chi² = 1.70, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.58 (P < 0.00001)

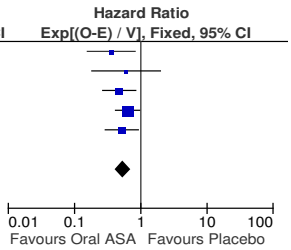


Figure 225: Adverse events

Study or Subgroup	Oral ASA Events	Oral ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DISSANAYAKE1973	3	33	0	31	1.4%	6.59 [0.35, 122.60]
HANAUER1996A	36	87	34	87	93.3%	1.06 [0.74, 1.52]
WRIGHT1993	12	49	2	52	5.3%	6.37 [1.50, 27.01]
Total (95% CI)		**169**		**170**	**100.0%**	**1.42 [1.00, 2.01]**
Total events	51		36			

Heterogeneity: Chi² = 7.72, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 1.98 (P = 0.05)

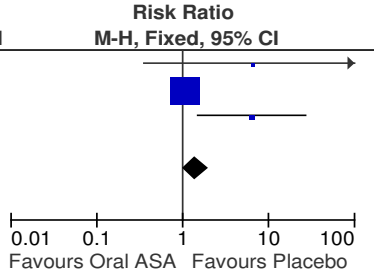


Figure 226: Serious adverse events

Study or Subgroup	Oral ASA Events	Oral ASA Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
HANAUER1996A	1	87	1	87	100.0%	1.00 [0.06, 16.12]
Total (95% CI)		**87**		**87**	**100.0%**	**1.00 [0.06, 16.12]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

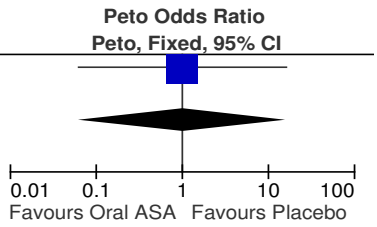
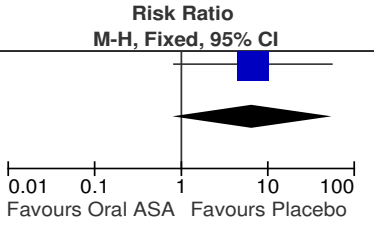


Figure 227: Hospitalisations

Study or Subgroup	Oral ASA Events	Oral ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HAWKEY1997	6	99	1	111	100.0%	6.73 [0.82, 54.91]
Total (95% CI)		**99**		**111**	**100.0%**	**6.73 [0.82, 54.91]**
Total events	6		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.08)



1.4.4 Oral aminosalicylates dose comparison

1.4.4.1 Mesalazine (Asacol)

Figure 228: Relapse (RR)

Study or Subgroup	Low dose Events	Total	High dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.2 1.2g versus 2.4g Asacol at 12 months						
PAOLUZI2005	48	76	48	80	100.0%	1.05 [0.82, 1.35]
Subtotal (95% CI)		**76**		**80**	**100.0%**	**1.05 [0.82, 1.35]**
Total events	48		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.69)						

Test for subgroup differences: Not applicable

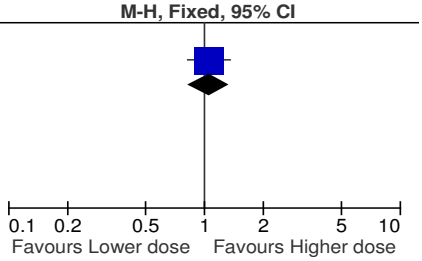


Figure 229: Relapse by frequency of relapses in the previous year (RR)

Study or Subgroup	Low dose Events	Total	High dose Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 1.2g versus 2.4g Asacol (≤3 relapses/ year)						
PAOLUZI2005	16	36	0	16	100.0%	15.16 [0.97, 238.19]
Subtotal (95% CI)		**36**		**16**	**100.0%**	**15.16 [0.97, 238.19]**
Total events	16		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
2.2.2 1.2g versus 2.4g Asacol (>3 relapses/year)						
PAOLUZI2005	32	40	48	64	100.0%	1.07 [0.86, 1.32]
Subtotal (95% CI)		**40**		**64**	**100.0%**	**1.07 [0.86, 1.32]**
Total events	32		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						

Test for subgroup differences: $Chi^2 = 3.55$, df = 1 (P = 0.06), $I^2 = 71.8\%$

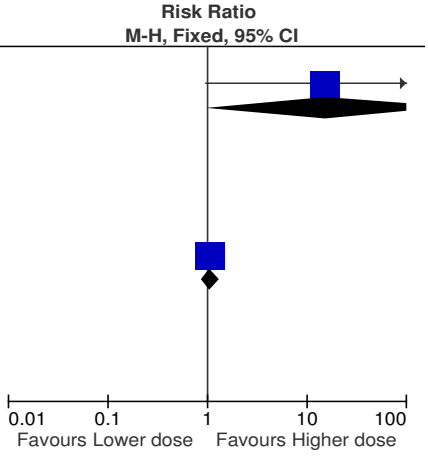
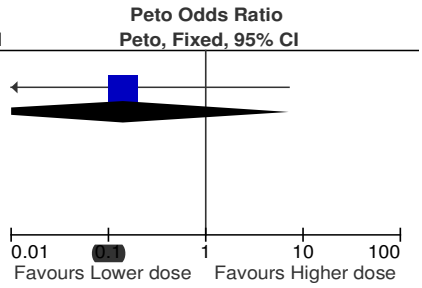


Figure 230: Adverse events

Study or Subgroup	Low dose Events	Total	High dose Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.4.2 1.2g versus 2.4g Asacol						
PAOLUZI2005	0	76	1	80	100.0%	0.14 [0.00, 7.18]
Subtotal (95% CI)		**76**		**80**	**100.0%**	**0.14 [0.00, 7.18]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						



1.4.4.2 Mesalazine (Salofalk)

Figure 231: Relapse (RR)

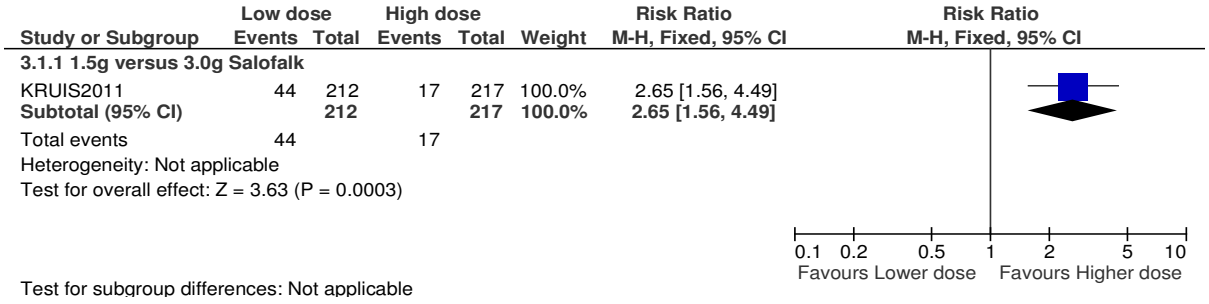


Figure 232: Adverse events

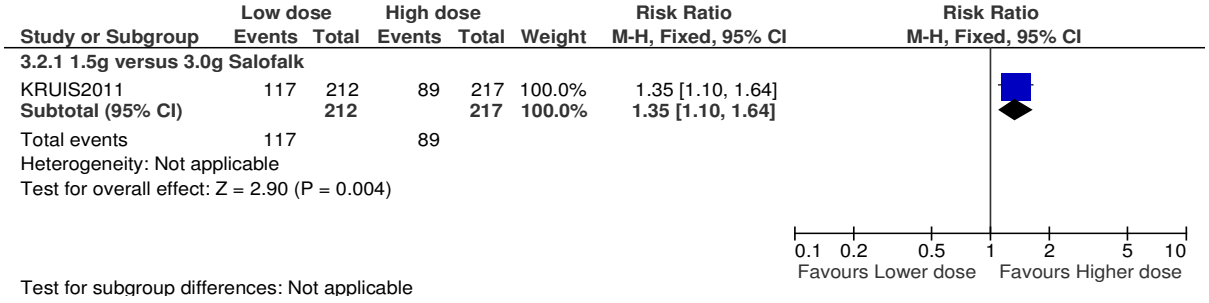
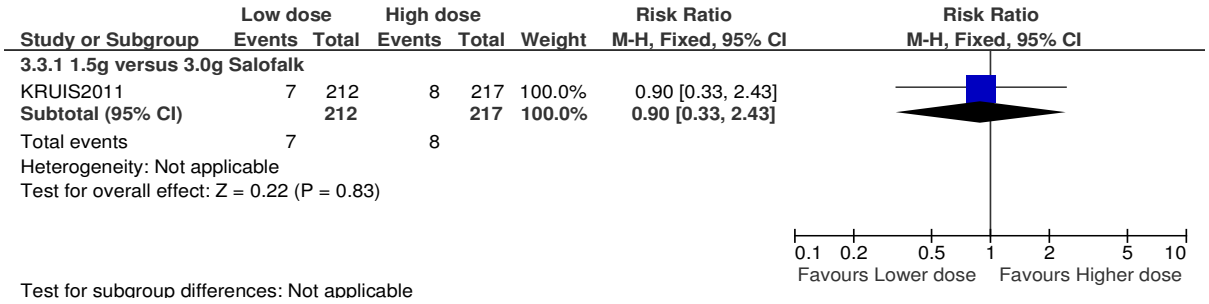


Figure 233: Serious adverse events



1.4.4.3 Olsalazine

Figure 234: Relapse (RR)

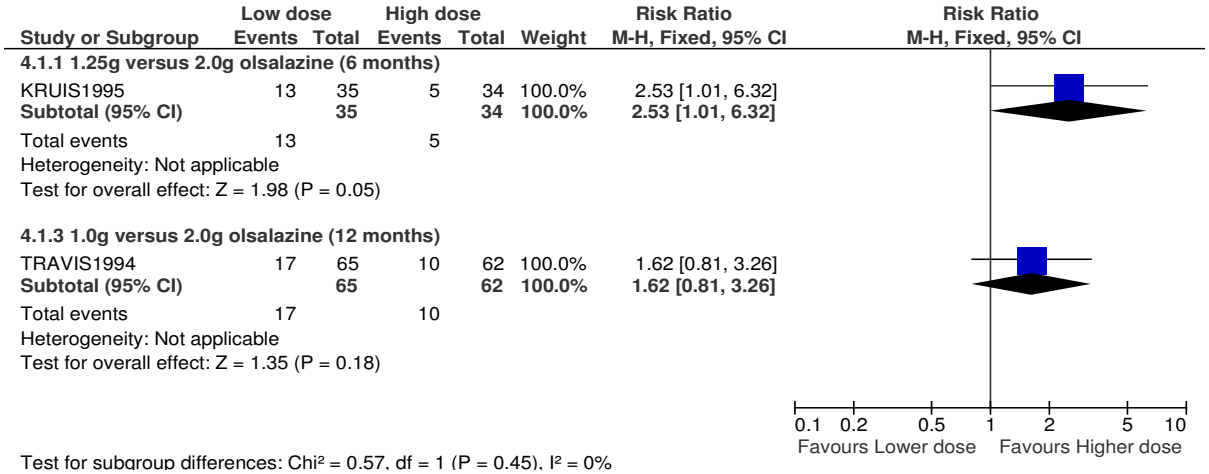
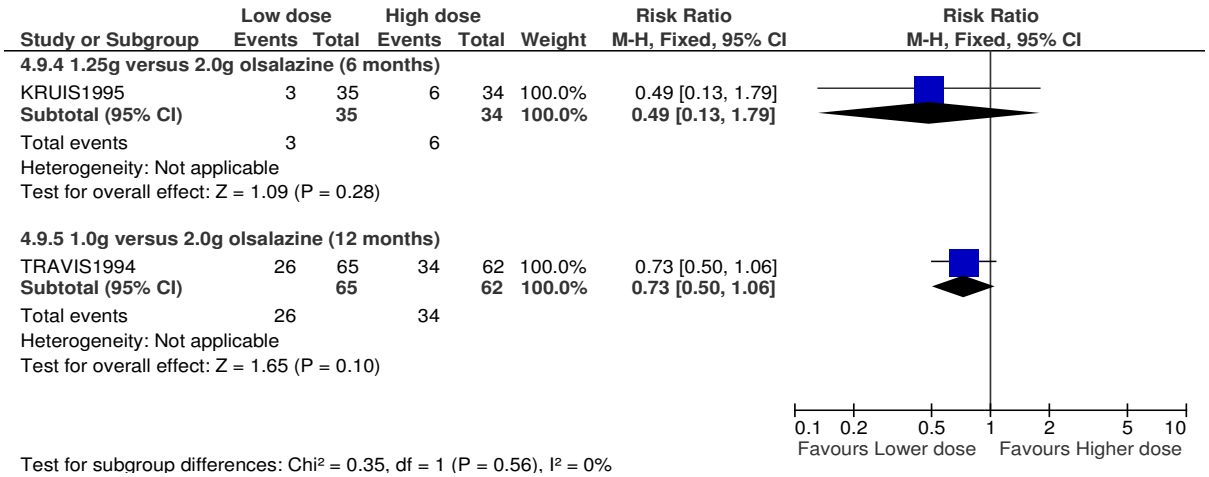
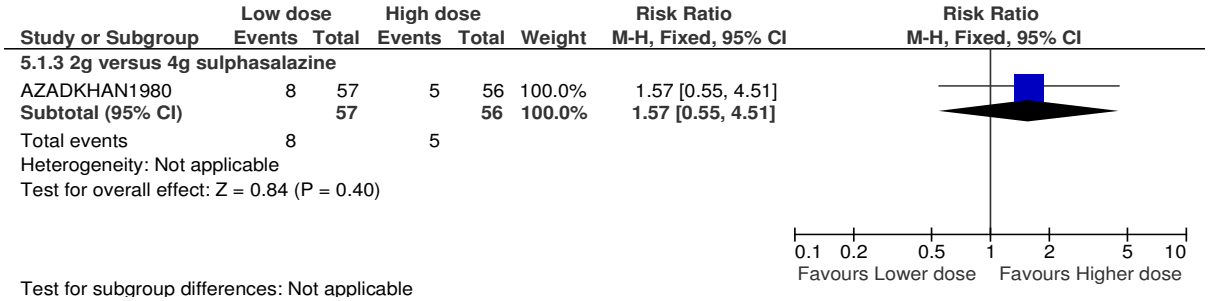


Figure 235: Adverse events



1.4.4.4 Sulphasalazine

Figure 236: Relapse (RR)



1.4.4.5 Balsalazide

Figure 237: Relapse (RR)

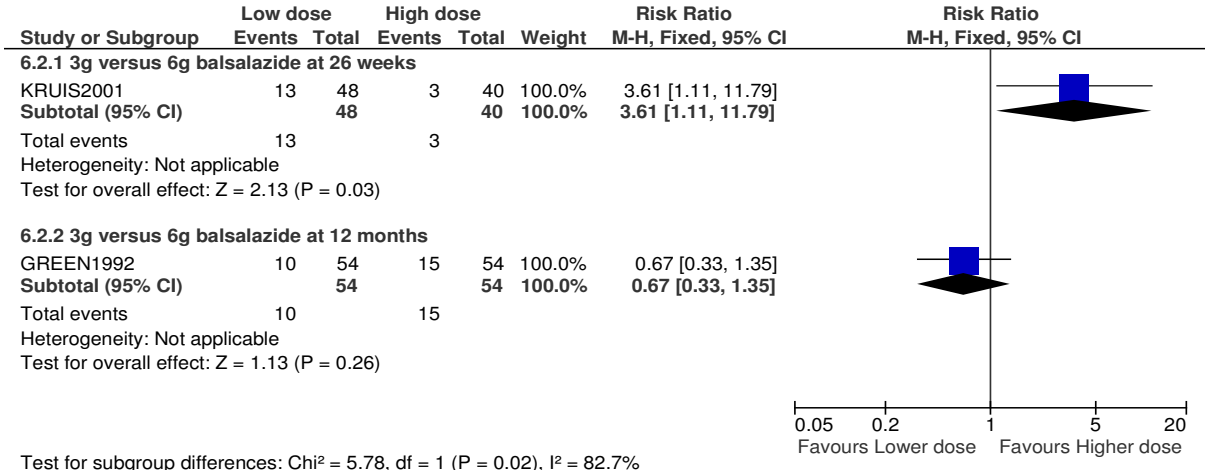
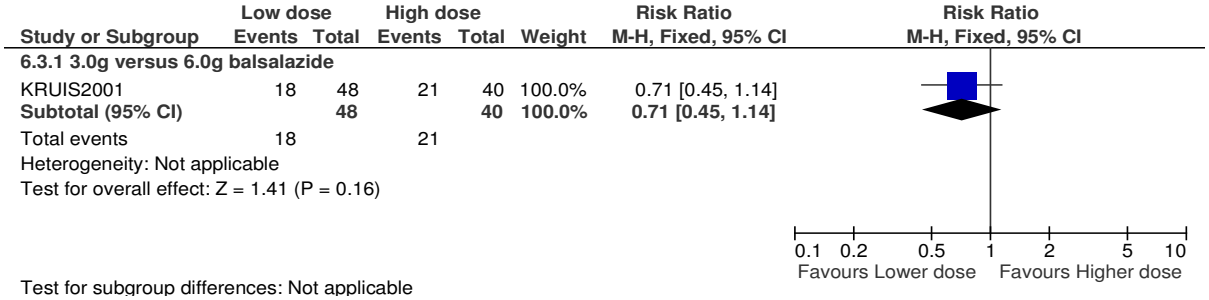


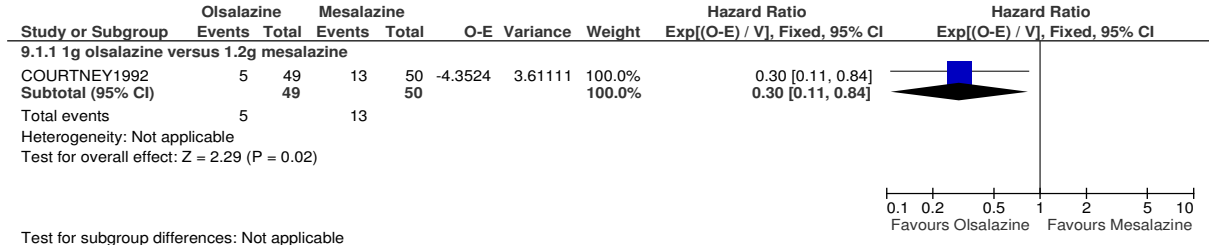
Figure 238: Adverse events



1.4.5 Interclass comparisons

1.4.5.1 Olsalazine versus mesalazine

Figure 239: Relapse (HR)



1.4.5.2 Olsalazine versus sulphasalazine

Figure 240: Relapse (HR)

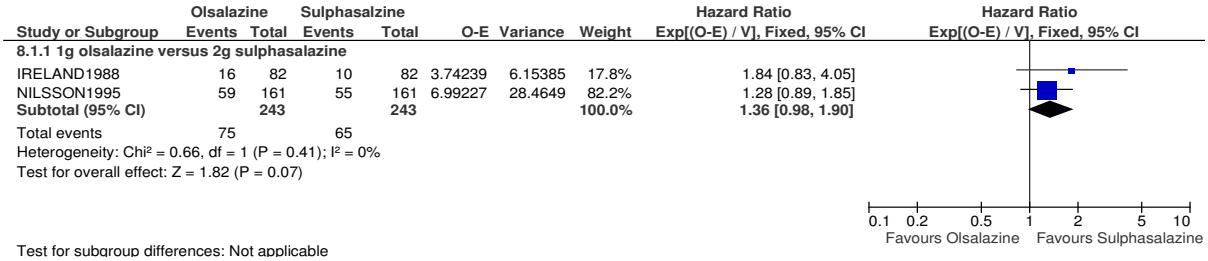


Figure 241: Relapse (RR)

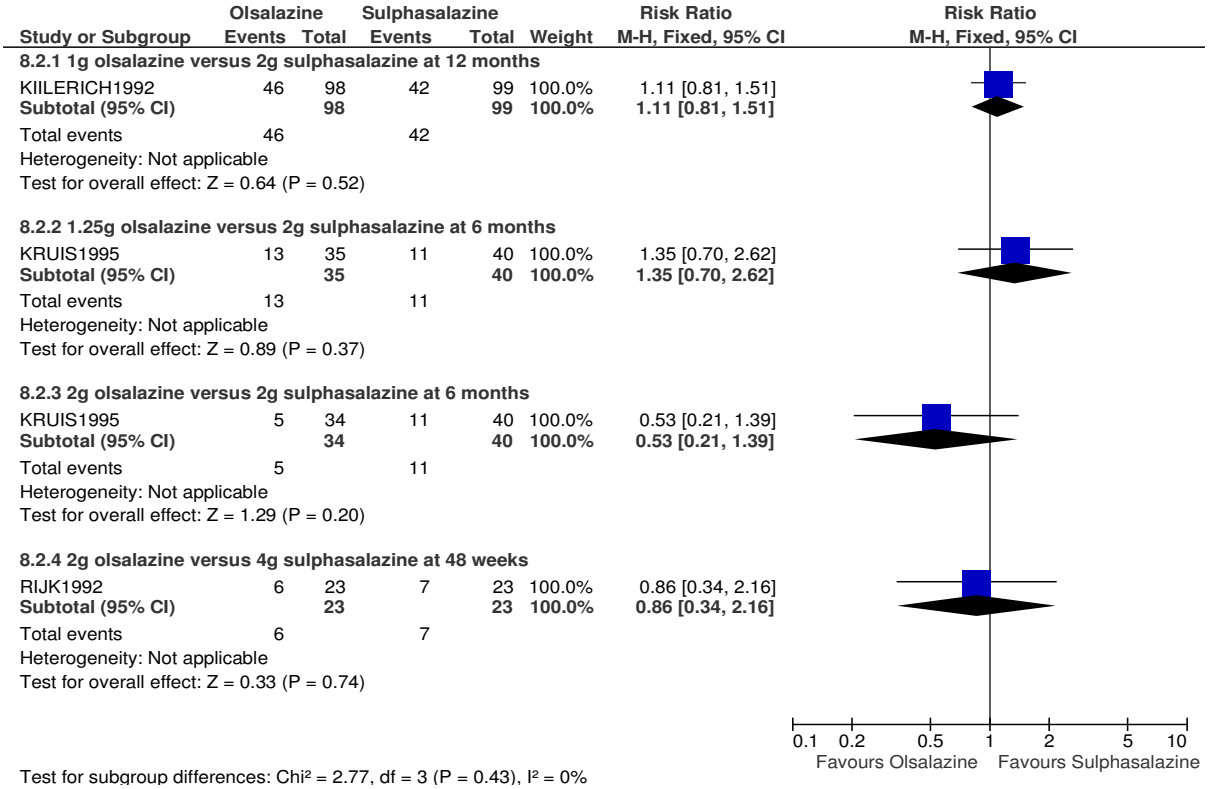


Figure 242: Adverse events

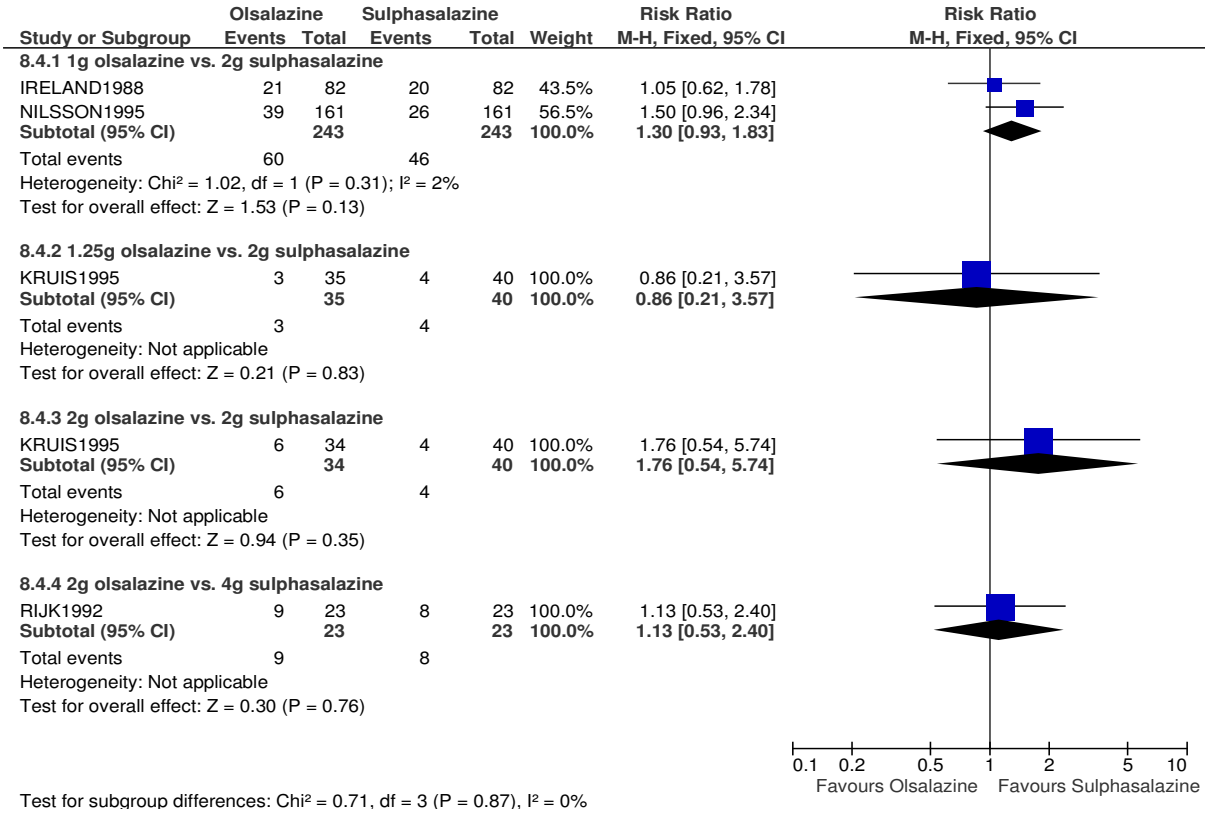
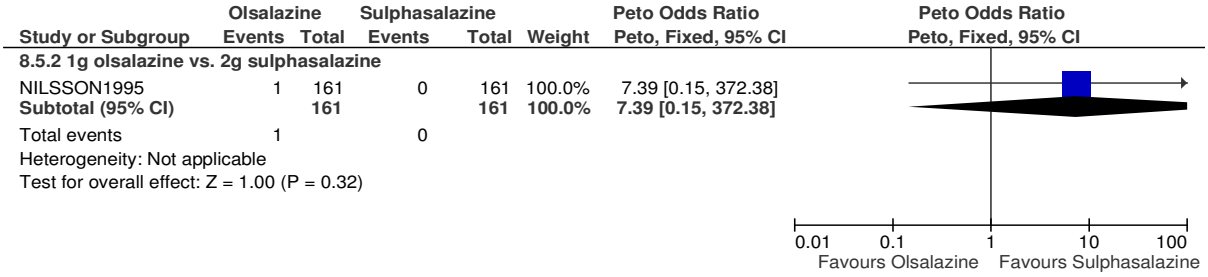
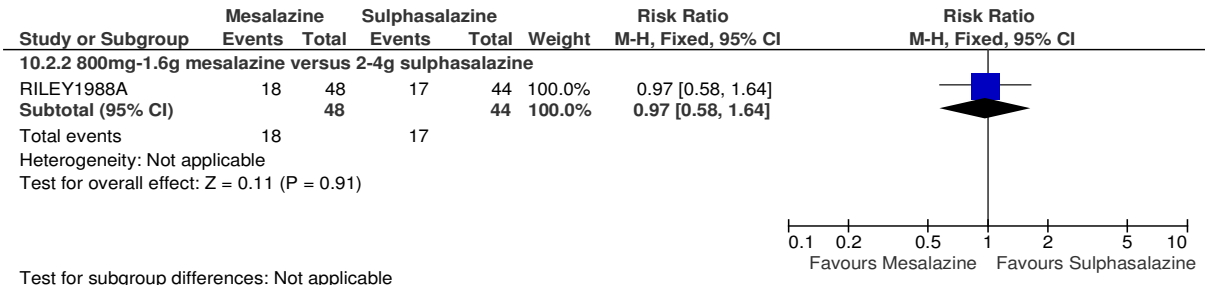


Figure 243: Serious adverse events



1.4.5.3 Mesalazine versus sulphasalazine

Figure 244: Relapse (RR)



1.4.5.4 Balsalazide versus mesalazine

Figure 245: Relapse (HR)

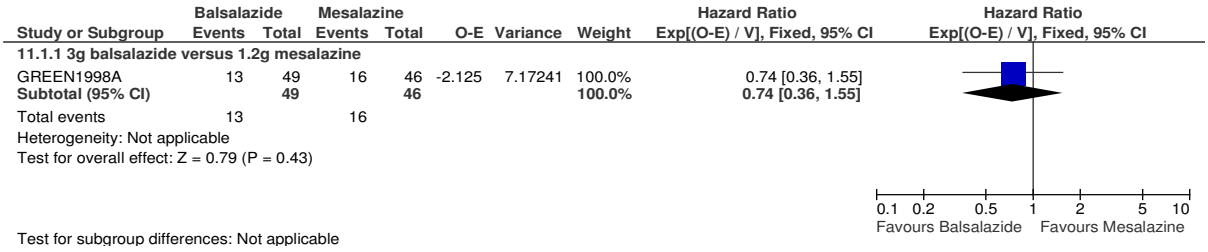


Figure 246: Relapse (RR)

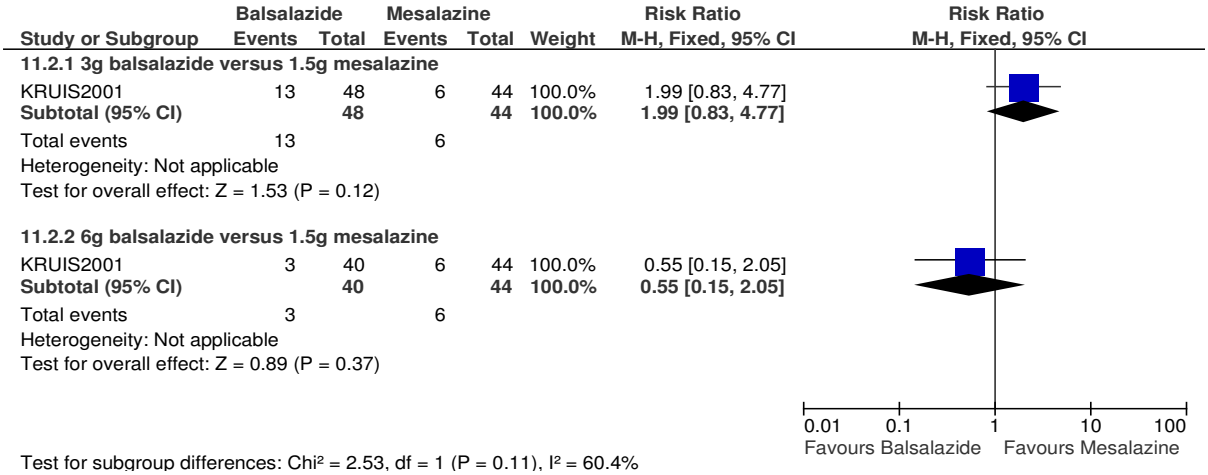


Figure 247: Adverse events

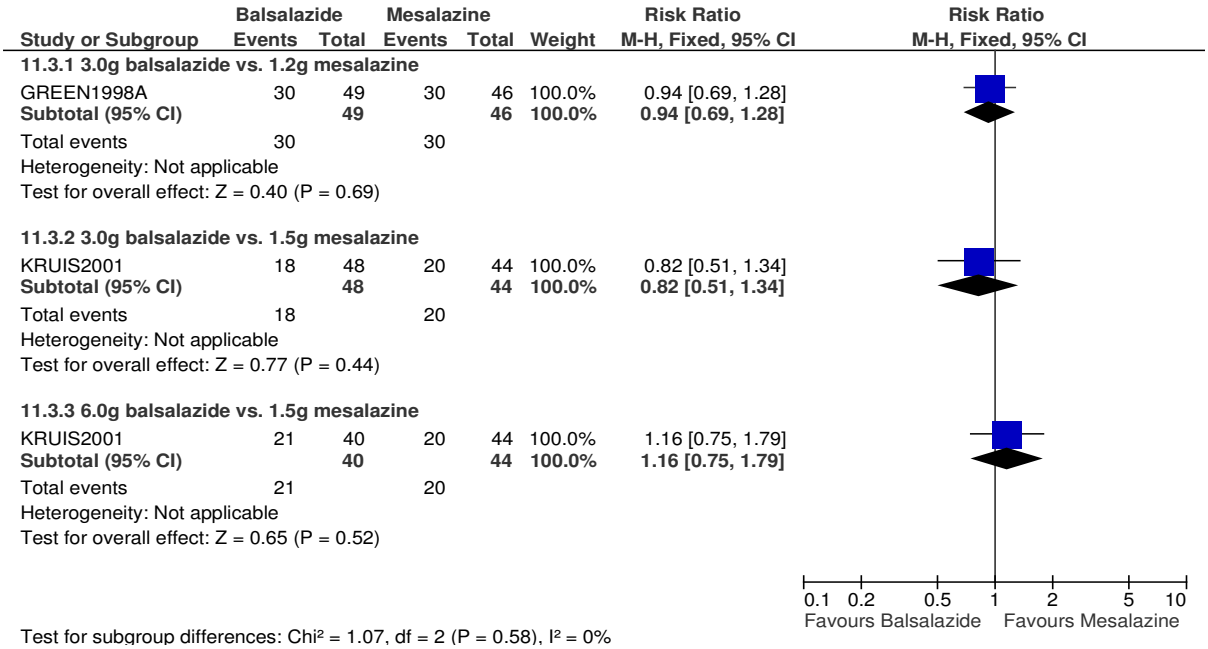
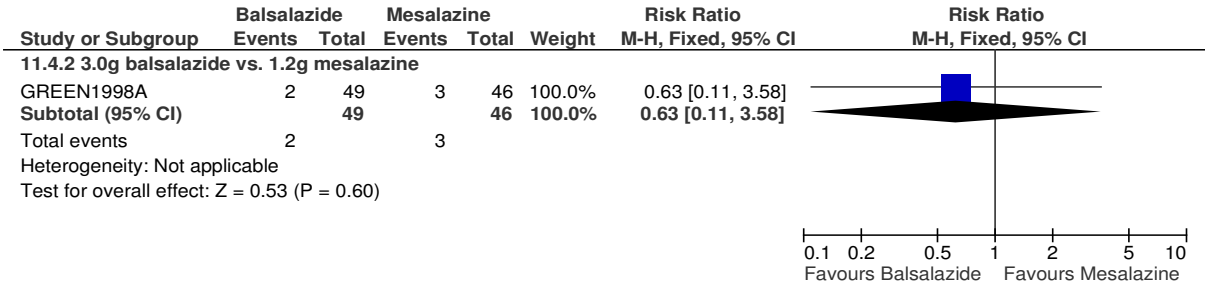


Figure 248: Serious adverse events



1.4.5.5 Mesalazine (Asacol) versus mesalazine (MEZAVANT XL)

Figure 249: Relapse (HR)

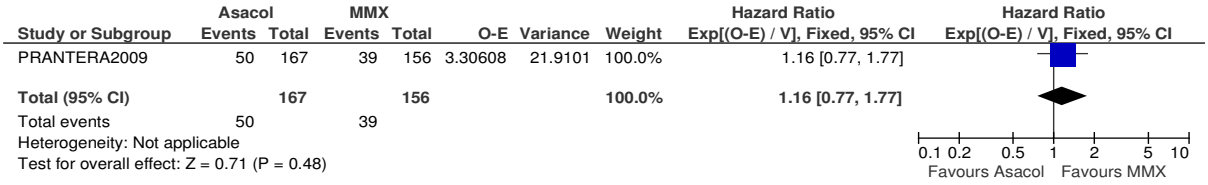


Figure 250: Adverse events

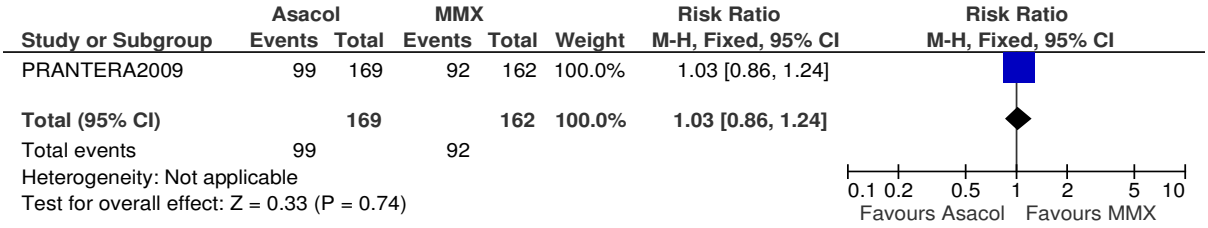
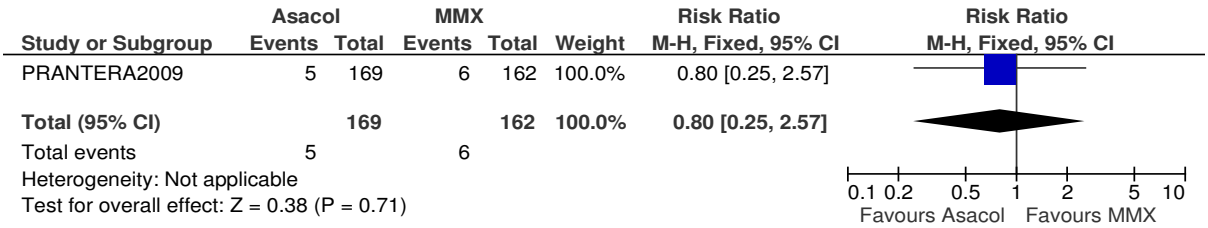


Figure 251: Serious adverse events



1.4.5.6 Mesalazine (Asacol) versus mesalazine (Pentasa)

Figure 252: Relapse (HR)

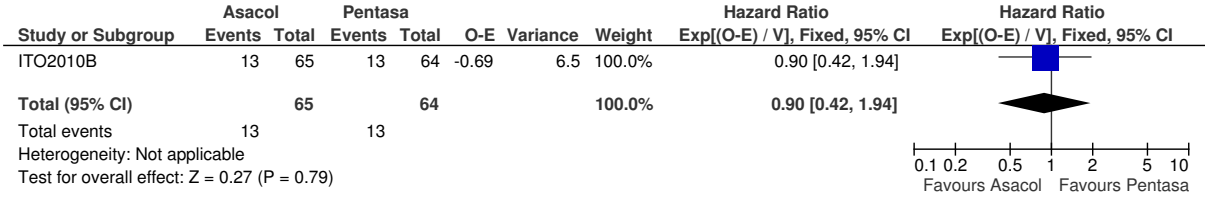


Figure 253: Adverse events

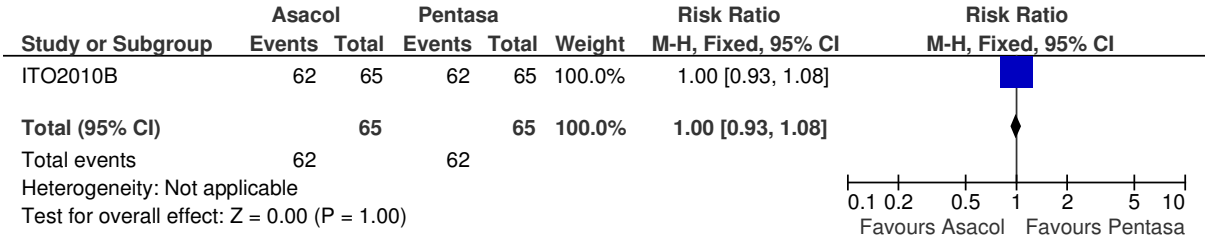
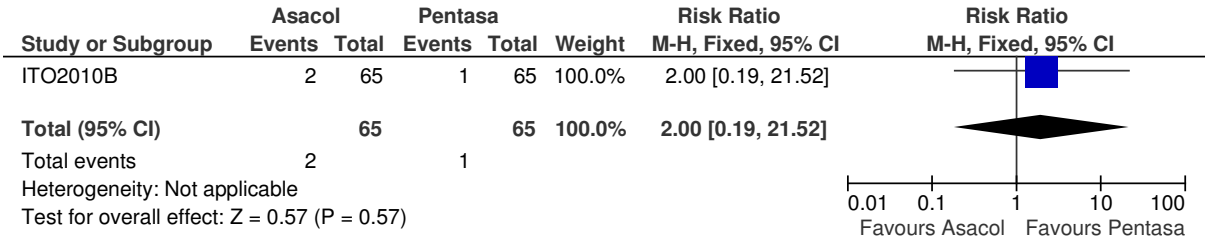


Figure 254: Serious adverse events



1.4.6 Regimen comparison

1.4.6.1 Once a day versus more than once a day

Figure 255: Relapse (HR)

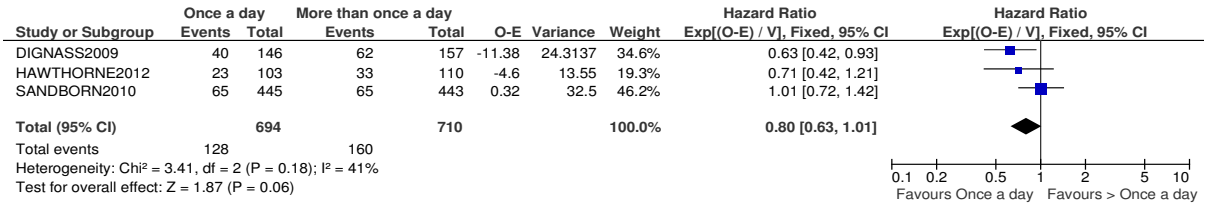


Figure 256: Relapse (RR)

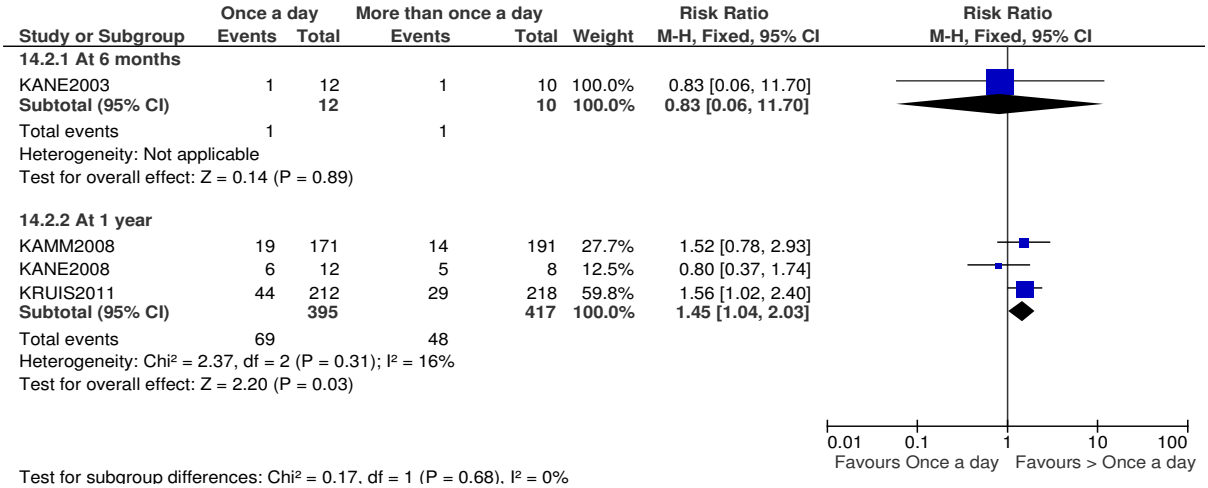


Figure 257: Adverse events

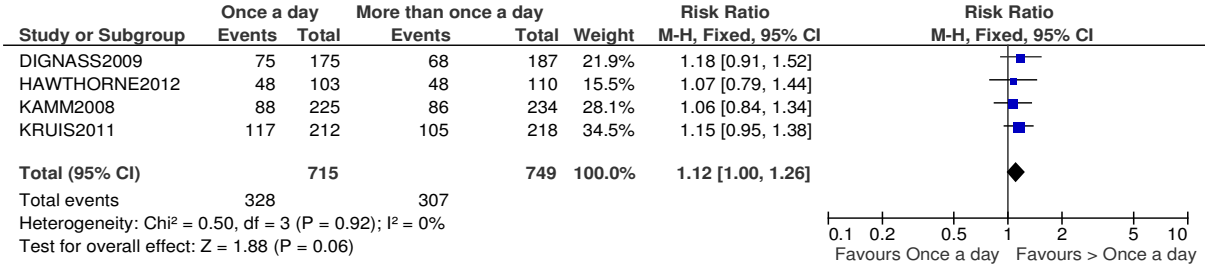
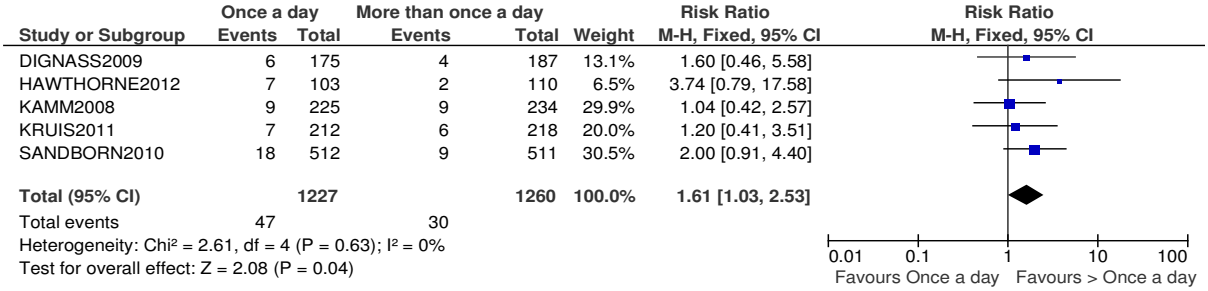


Figure 258: Serious adverse events



1.4.7 Regimen and dose comparison

1.4.7.1 Once a day, higher total dose versus twice a day, lower total dose

Figure 259: Relapse (HR)

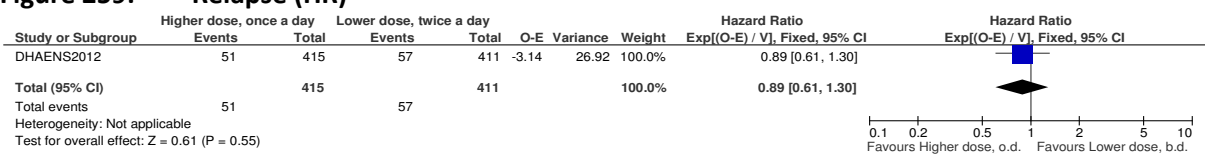
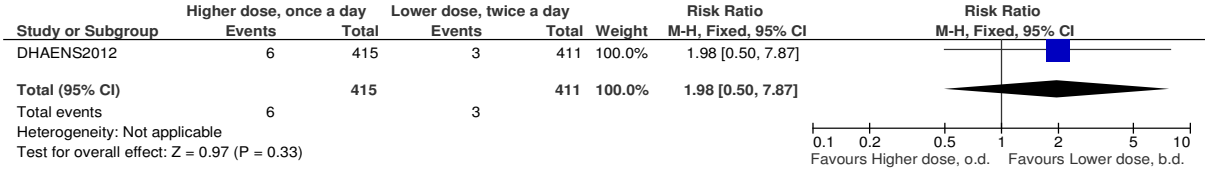


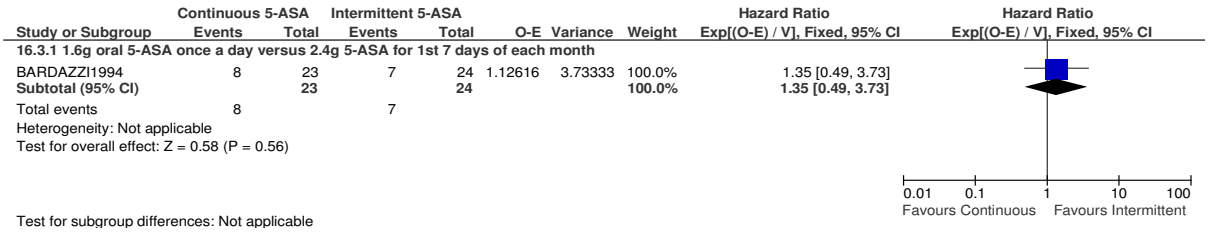
Figure 260: Serious adverse events



1.4.8 Regimen comparison

1.4.8.1 Continuous versus intermittent oral aminosalicylates

Figure 261: Relapse (HR)



1.4.9 Other combinations of oral and or topical aminosalicylates

1.4.9.1 Continuous oral aminosalicylates versus intermittent topical aminosalicylates

Figure 262: Relapse (HR)

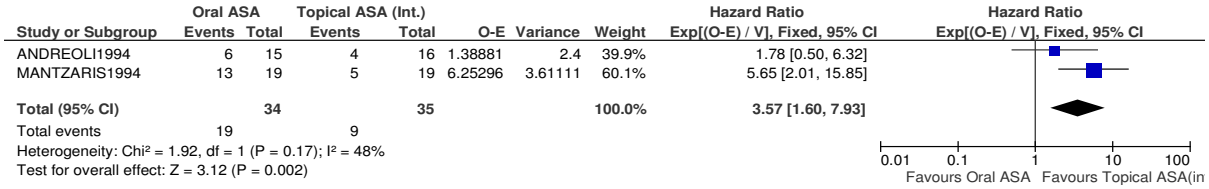


Figure 263: Adverse events

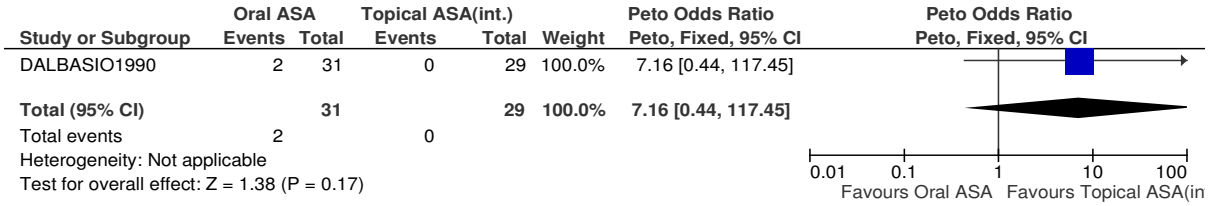
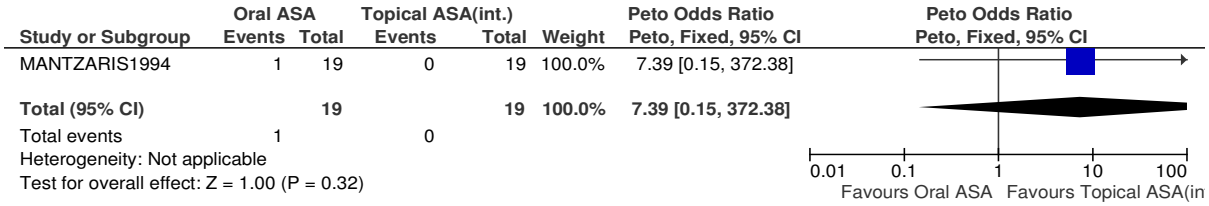
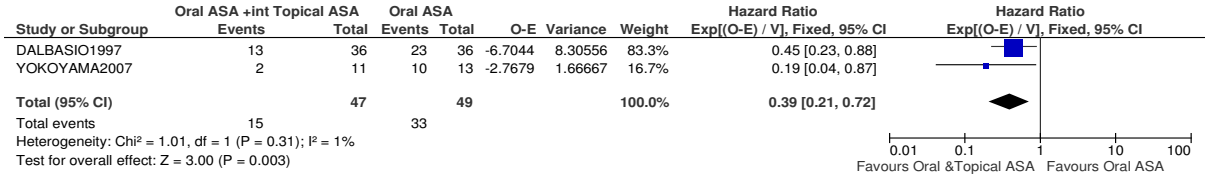


Figure 264: Colectomy



1.4.9.2 Continuous oral aminosalicylates & intermittent topical aminosalicylates versus continuous oral aminosalicylates

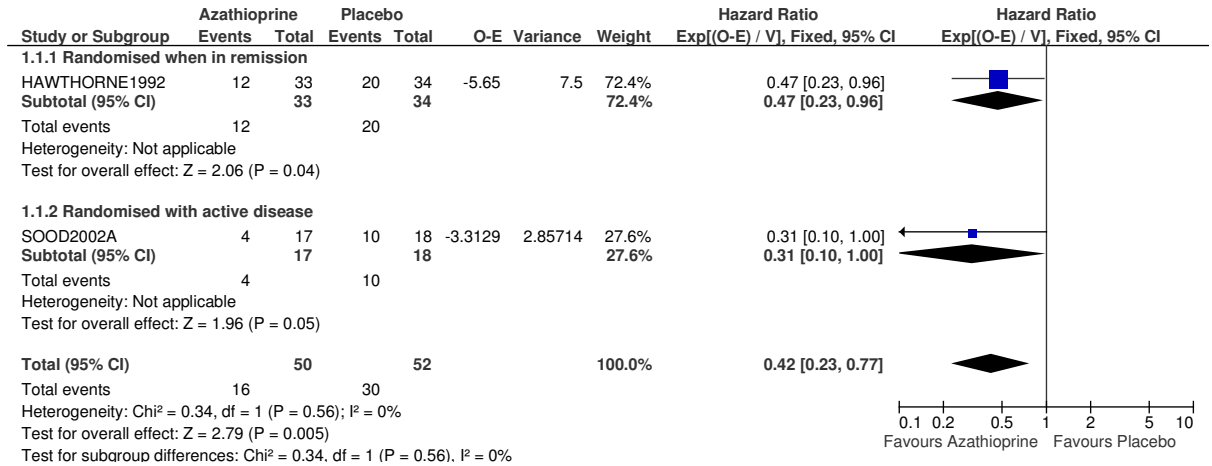
Figure 265: Relapse (HR)



1.4.10 Immunomodulators

1.4.10.1 Azathioprine versus placebo

Figure 266: Relapse (HR)



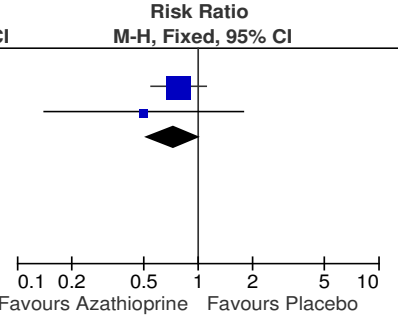
Note: HAWTHORNE1992- withdrawal study , some patients also took oral aminosalicylates, SOOD2002A- in addition to steroids and sulphasalazine in both arms.

Figure 267: Relapse at 1 year (RR)

Study or Subgroup	Azathioprine Events	Azathioprine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.2 Randomised with active disease						
JEWELL1974	21	37	24	33	80.9%	0.78 [0.55, 1.11]
SOOD2000	3	25	6	25	19.1%	0.50 [0.14, 1.78]
Subtotal (95% CI)		**62**		**58**	**100.0%**	**0.73 [0.51, 1.04]**
Total events	24		30			

Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)

Test for subgroup differences: Not applicable

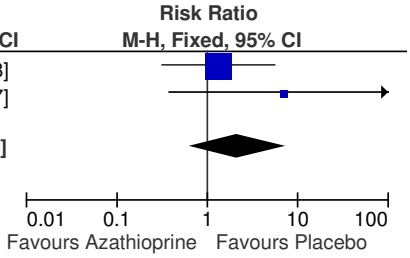


Note: JEWELL1974- in addition to steroids in both arm, SOOD2000- in addition to steroids and sulphasalazine in both arms

Figure 268: Adverse events

Study or Subgroup	Azathioprine Events	Azathioprine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
JEWELL1974	4	40	3	40	85.7%	1.33 [0.32, 5.58]
SOOD2000	3	25	0	25	14.3%	7.00 [0.38, 128.87]
Total (95% CI)		**65**		**65**	**100.0%**	**2.14 [0.63, 7.30]**
Total events	7		3			

Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² = 5%
Test for overall effect: Z = 1.22 (P = 0.22)



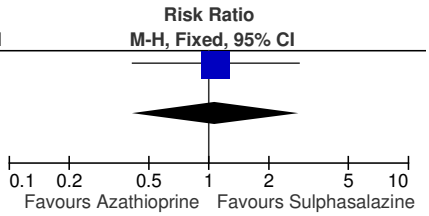
Note: JEWELL1974- in addition to steroids in both arm, SOOD2000- in addition to steroids and sulphasalazine in both arms.

1.4.10.2 Azathioprine versus sulphasalazine

Figure 269: Relapse at 18 months (RR)

Study or Subgroup	Azathioprine Events	Azathioprine Total	Sulphasalazine Events	Sulphasalazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SOOD2003	5	12	5	13	100.0%	1.08 [0.41, 2.83]
Total (95% CI)		**12**		**13**	**100.0%**	**1.08 [0.41, 2.83]**
Total events	5		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)

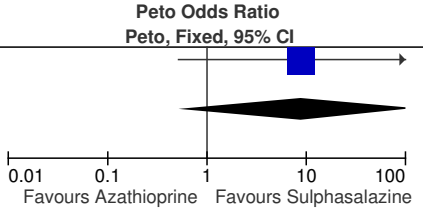


Note: Steroids were also taken in both arms

Figure 270: Adverse events

Study or Subgroup	Azathioprine Events	Azathioprine Total	Sulphasalazine Events	Sulphasalazine Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
SOOD2003	2	12	0	13	100.0%	8.79 [0.52, 149.55]
Total (95% CI)		**12**		**13**	**100.0%**	**8.79 [0.52, 149.55]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)



Note: Steroids were also taken in both arms

1.4.10.3 Azathioprine versus azathioprine & olsalazine

Figure 271: Relapse at different time points (RR)

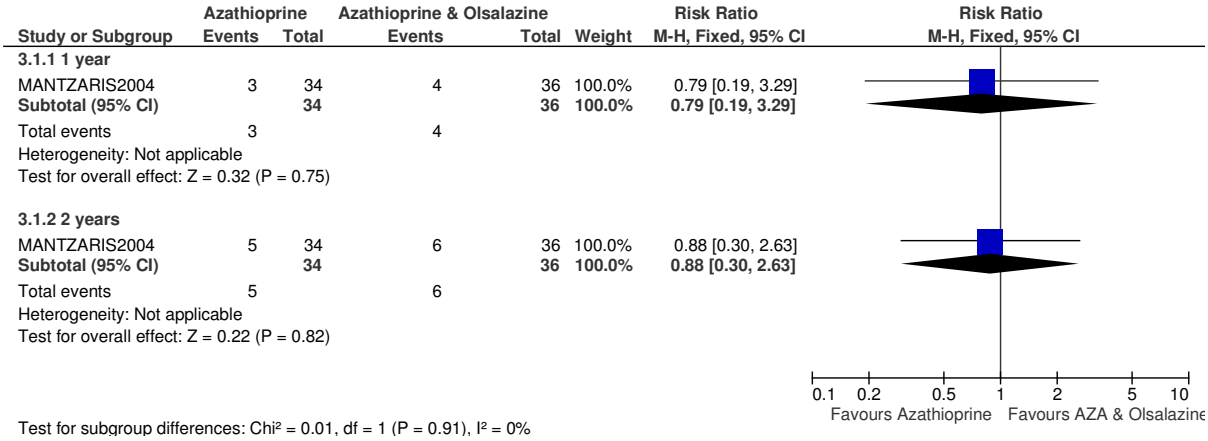
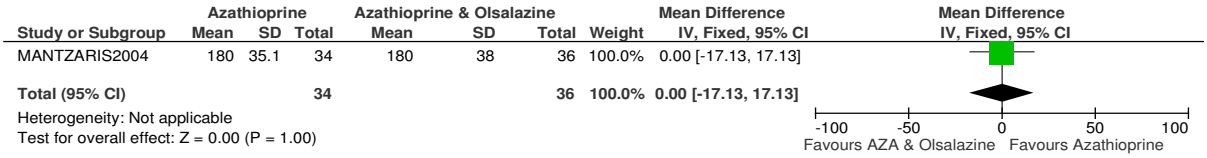
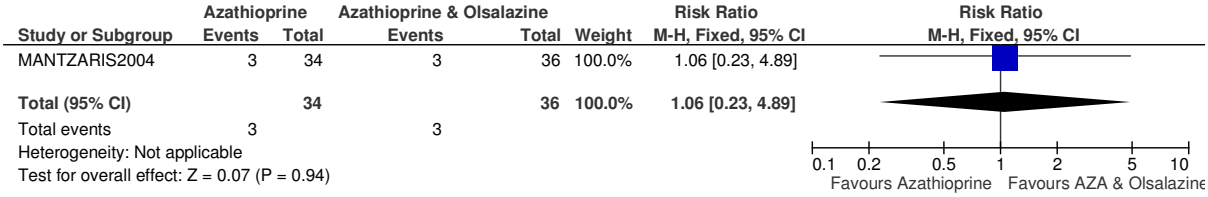


Figure 272: Quality of life - IBDQ (better indicated by higher values)



Note: Steroid dependent ulcerative colitis. MIDs: +/- 3.965

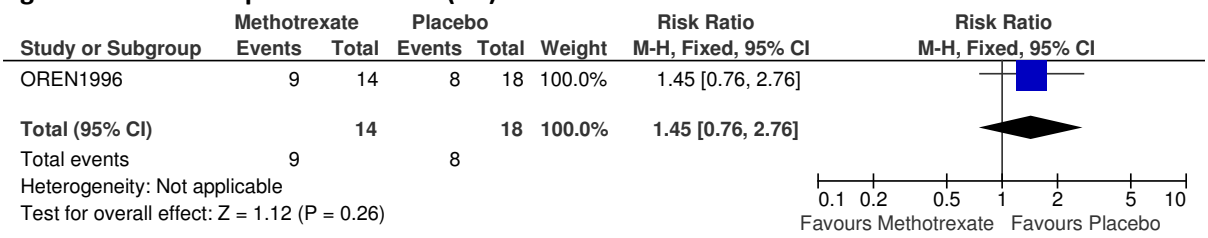
Figure 273: Serious adverse events



Note: Steroid dependent ulcerative colitis.

1.4.10.4 Methotrexate versus placebo

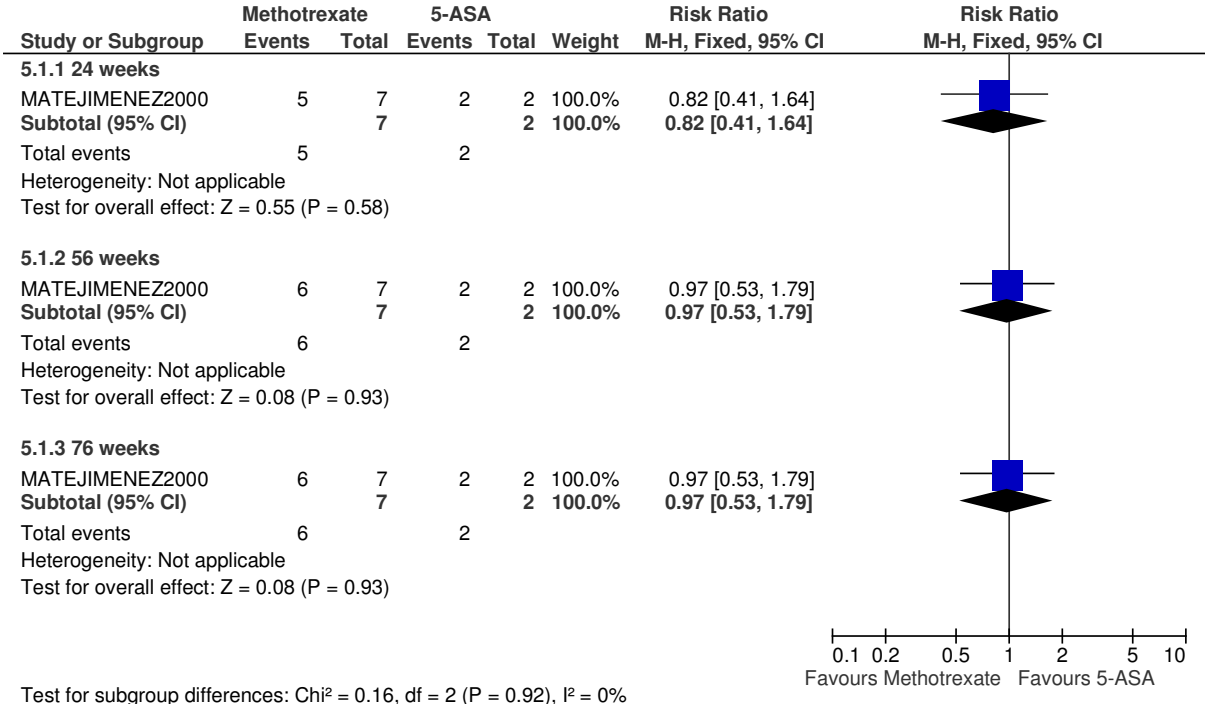
Figure 274: Relapse at 9 months (RR)



Note: Some patients were also on mesalazine and/or steroids.

1.4.10.5 Methotrexate versus 5-aminosalicylic acid

Figure 275: Relapse at different time points (RR)

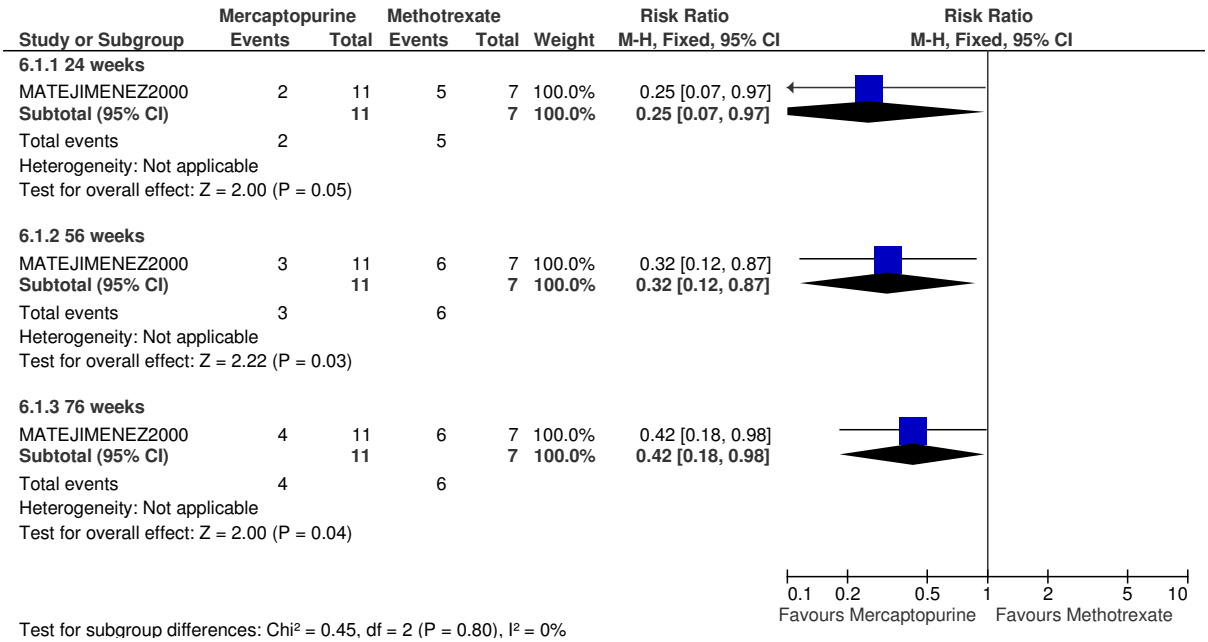


Test for subgroup differences: Chi² = 0.16, df = 2 (P = 0.92), I² = 0%

Note: In addition to steroids in both arms.

1.4.10.6 Mercaptopurine versus methotrexate

Figure 276: Relapse at different time points (RR)

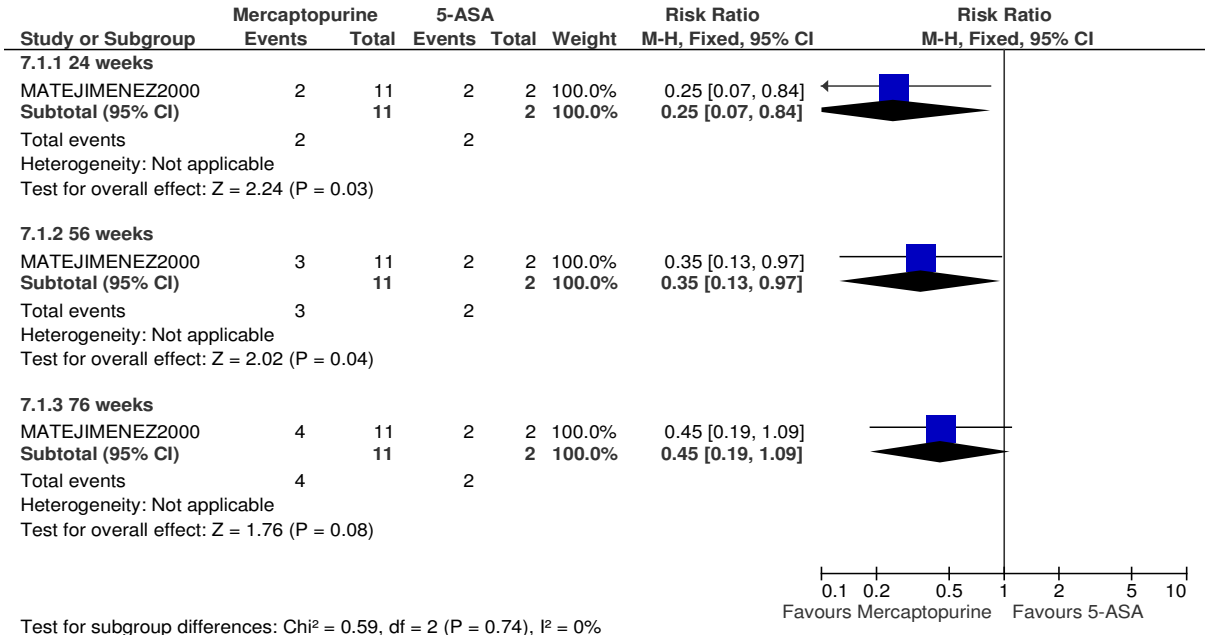


Test for subgroup differences: Chi² = 0.45, df = 2 (P = 0.80), I² = 0%

Note: In addition to steroids in both arms.

1.4.10.7 Mercaptopurine versus 5-aminosalicylic acid

Figure 277: Relapse at different time points (RR)



Test for subgroup differences: $Chi^2 = 0.59$, df = 2 (P = 0.74), $I^2 = 0\%$

Note: In addition to steroids in both arms.

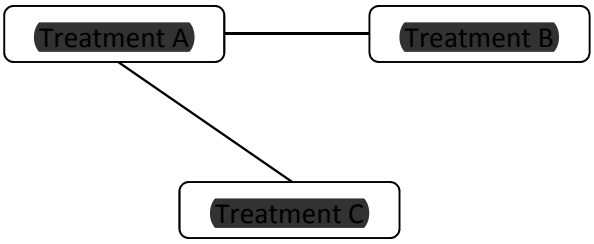
2 Appendix I: Induction NMA

Please note that evidence on treatments for inducing remission in people with mild-to-moderate ulcerative colitis was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

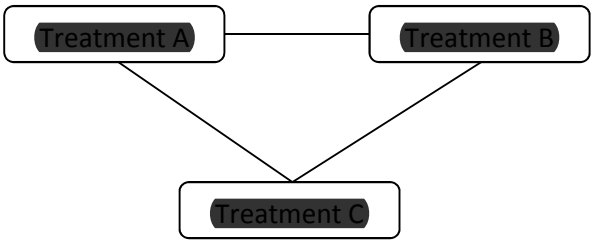
2.1

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in Chapter 5 and the Forest plots in Appendix H) does not help inform which intervention is the most effective for the induction of remission of mild to moderate left-sided/extensive ulcerative colitis in adults. The challenge of interpretation has arisen for three reasons:

- In isolation, each pair-wise comparison (for example; oral mesalazine versus oral balsalazide) does not inform the choice among different oral, topical or combination treatments.
- Direct evidence is not available for some pair-wise comparisons in randomised controlled trials (for example; oral mesalazine versus oral sulphasalazine). In the example below there are no trials looking at treatment B versus treatment C.



- There are frequently multiple overlapping comparisons known as "closed loops" in the NMA where the estimates of an effect have been calculated either within the same trial or from multiple trials. Different trials may give slightly different point estimates



To overcome these issues, a hierarchical Bayesian Network Meta-analysis (NMA) was performed. This type of analysis allows the synthesis of data from direct and indirect comparisons without breaking randomisation and the ranking of different interventions. Two NMAs have been run, the first being the baseline scenario and the second which combined aminosalicylates together into low and high doses.

For the baseline NMA, in order of efficacy, the following networks have been reviewed:

- The proportion of people who are in clinical remission (author definition) at the end of the trial (≤12 weeks)
- The proportion of people who have had clinical improvement (author definition) at the end of the trial(≤12 weeks)
- The proportion of people who have withdrawn from treatment due to adverse events(≤12 weeks)

For the combined NMA, the following networks have been reviewed:

- The proportion of people who are in clinical remission (author definition) at the end of the trial (≤12 weeks)
- The proportion of people who have withdrawn from treatment due to adverse events(≤12 weeks)

The analysis provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

2.2 Methods

2.2.1 Study selection and data collection

To estimate the relative risks of different treatments used for the induction of remission, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular induction of remission strategy was derived only from randomised controlled trials that had that particular treatment in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on selected studies that matched the pre-defined NMA protocol. Doses of the drugs in the included RCTs were classed as low and high as indicated by the range of the doses in the British National Formulary (BNF).

Therefore, three networks of evidence were identified, defined by population and outcome measure.

For adults, young people and children with mild/moderate left sided/extensive ulcerative colitis:

- Network 1: Proportion of people achieving clinical remission by the end of the trial (≤12 weeks)
- Network 2: Proportion of people achieving clinical improvement by the end of the trial(≤12 weeks)

- Network 3: Proportion of people withdrawing from treatment due to adverse events by the end of the trial(≤12 weeks)

To review the NMA protocol, see Appendix C.

2.2.2 Outcome measures

The NMA evidence reviews considered two clinical efficacy outcomes at up to 12 weeks of treatment identified from the clinical evidence review and considered by the GDG as the most important clinical outcomes. Withdrawals due to adverse events rather than drug related adverse events were chosen due to unclear reporting in the trials. Although this was not an outcome in the clinical review, it was chosen because it is thought to be the best approximate measure for this outcome.

2.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical review presented in Chapter 5 of the full guideline and the Forest plots in Appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the network meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded (see page 151, Excluded studies from the baseline NMA and page152, Additional excluded studies from the combined NMA).

The treatments included in each network for each NMA are shown in Table 1.

Table 1: Induction of remission treatments included in the network meta-analyses of people with mild/moderate left sided/ extensive ulcerative colitis

Baseline Network Meta-Analysis			Combined Network Meta-Analysis	
Network 1: Clinical remission	Network 2: Clinical improvement	Network 3: Withdrawals due to adverse events	Network 1: Clinical remission	Network 2: Withdrawals due to adverse events
Placebo	Placebo	Placebo	Placebo	Placebo
Low dose mesalazine	Low dose mesalazine	Low dose mesalazine	Low dose ASA	Low dose ASA
High dose mesalazine	High dose mesalazine	High dose mesalazine	High dose ASA	High dose ASA
High dose olsalazine	Low dose SASP	Low dose SASP	Oral prednisolone	Oral beclometasone
Oral prednisolone	High dose olsalazine	High dose olsalazine	Oral beclometasone	Mesalazine & beclometasone (oral)
Balsalazide	Balsalazide	Balsalazide	Mesalazine & beclometasone (oral)	Oral and topical mesalazine
Oral beclometasone	Oral beclometasone	Oral beclometasone	Oral and topical mesalazine	
Mesalazine & beclometasone (oral)	Mesalazine & beclometasone (oral)	Mesalazine & beclometasone (oral)		
Oral and topical mesalazine	Oral and topical mesalazine	Oral and topical mesalazine		
Low dose SASP				

2.2.4 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS version 1.4. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome a diagram of the evidence network was produced.

The model used was a random and fixed effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. Random effects models allow for the possibility that the true treatment effect may differ between trials. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000. When a trial has reported zero event in a treatment arm (zero cell count), then a constant value of 1.0 has been added to both the number of events and the total number of people completed this trial in all of the arms in order to preserve the proportional efficacy of the intervention compared to the control treatment in that trial and to obtain non-infinite estimates of treatment effects and non-infinite variance. If there were no events in any of the arms, the study was excluded.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance and deviance information criteria. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data at a satisfactory level.

The results, in terms of relative risk, of pair-wise meta-analyses are presented alongside the NMA indirect evidence results. They only include studies meeting the inclusion criteria so may differ slightly from the clinical evidence review (Chapter 5 and the Forest plots in Appendix H) meta-analyses.

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for the response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{OR}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\tilde{\theta} = Ln(\widetilde{OR}) + Ln(BO)$$

And:

$$p = \frac{e^{\tilde{\theta}}}{1 + e^{\tilde{\theta}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability (p_b) to get treatment specific relative risks (rr_b):

$$p_b = \frac{e^{BO}}{1 + e^{BO}}$$

$$rr_b = \frac{p}{p_b}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensure that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

Differences between treatments were considered significant at the 0.05 level if the 95% credible interval for the RR did not cross 1.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations (e.g. populations of mixed disease extent, age)
- Use of concomitant medications
- Different doses for drug treatments other than oral ASAs were the doses were not taken into account
- Different trial durations (longer trials are likely to have a higher proportion of patients achieving the outcome)
- Quality of the study (risk of bias)
- Different indexes and thresholds used to determine clinical remission and improvement

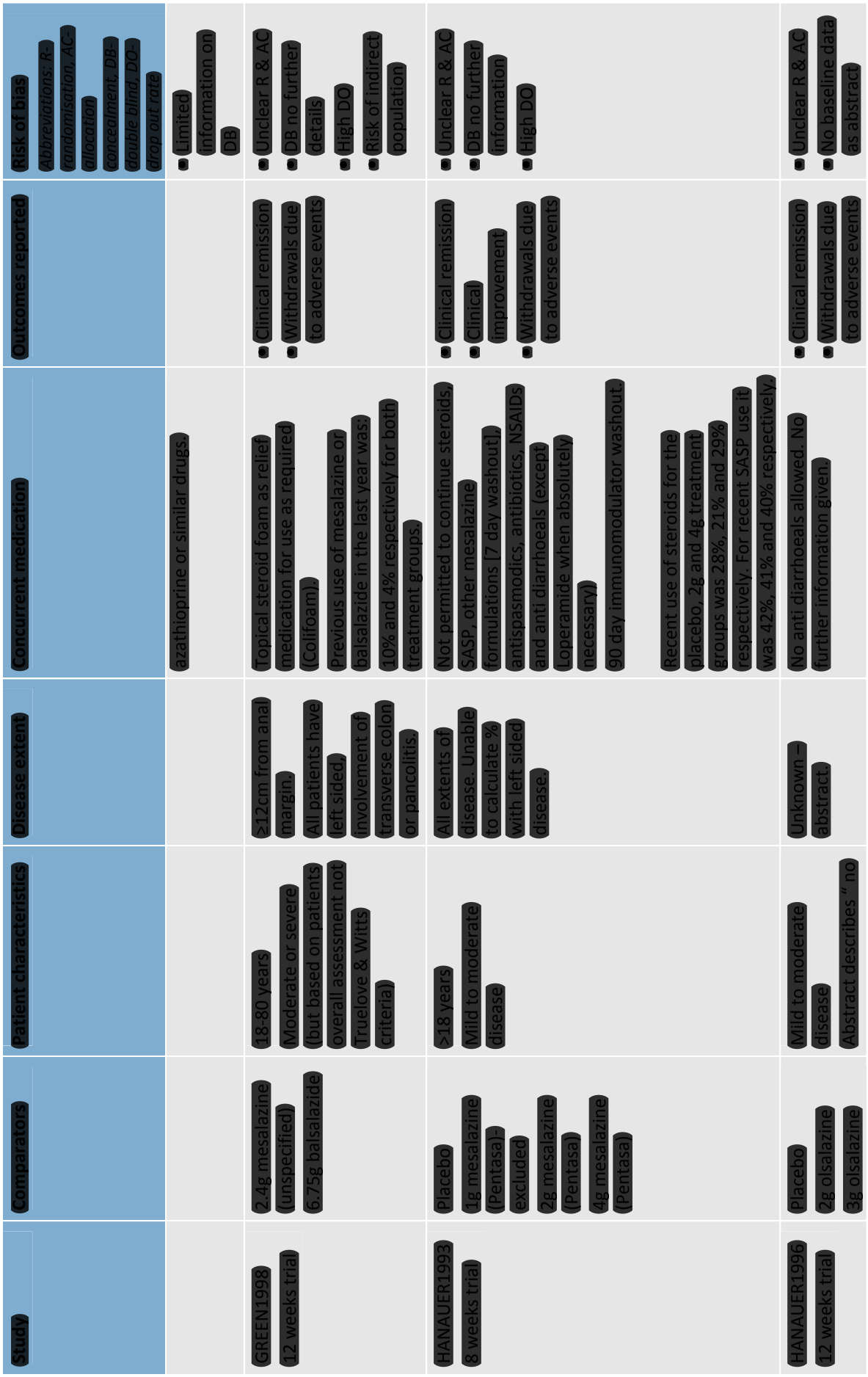
This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risk ratios from the direct evidence (from pair-wise meta-analysis) to the relative risk ratios from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the relative risk ratio from the NMA did not fit within the confidence interval of the relative risk ratio from the direct comparison.

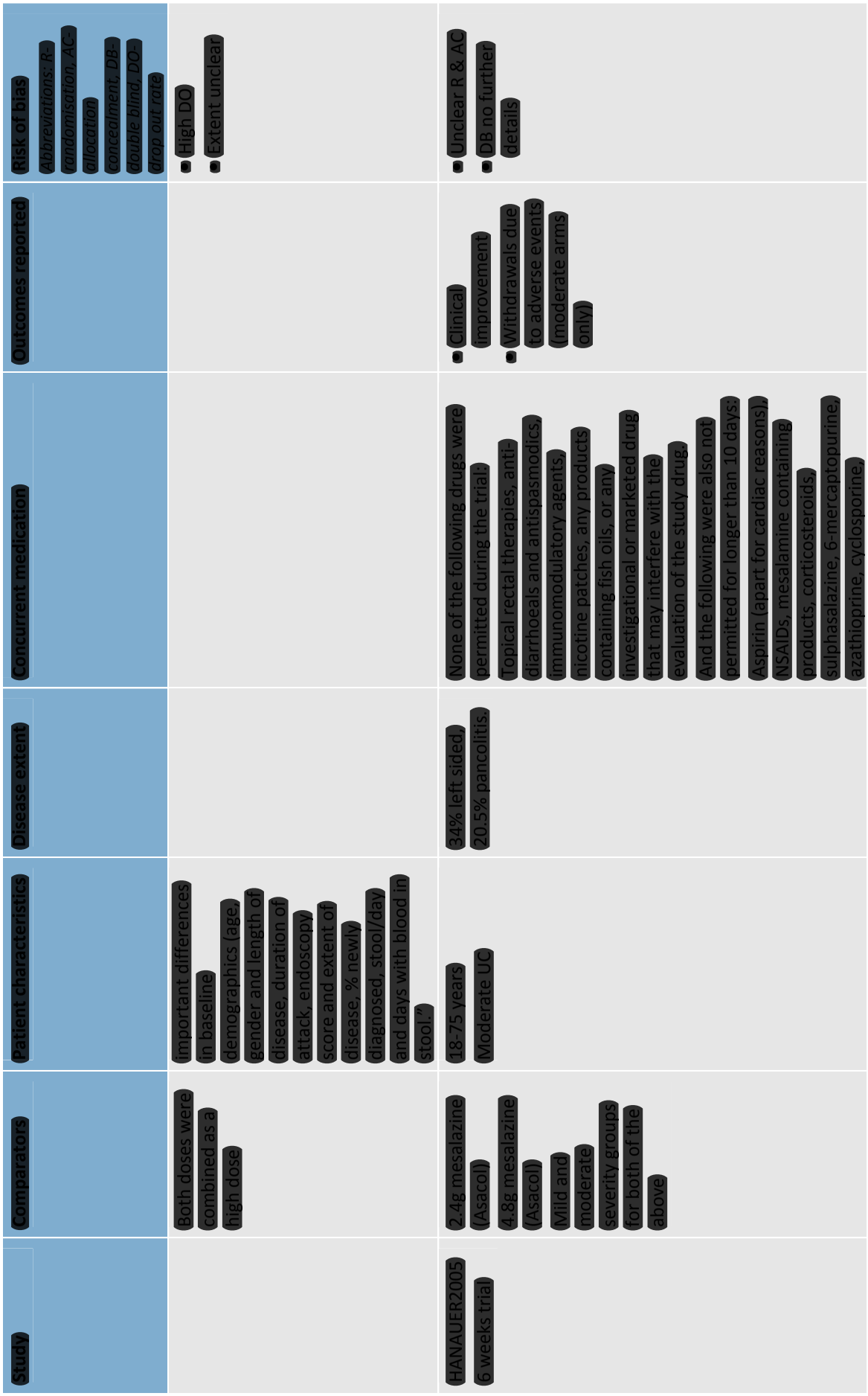
2.3 Baseline NMA results

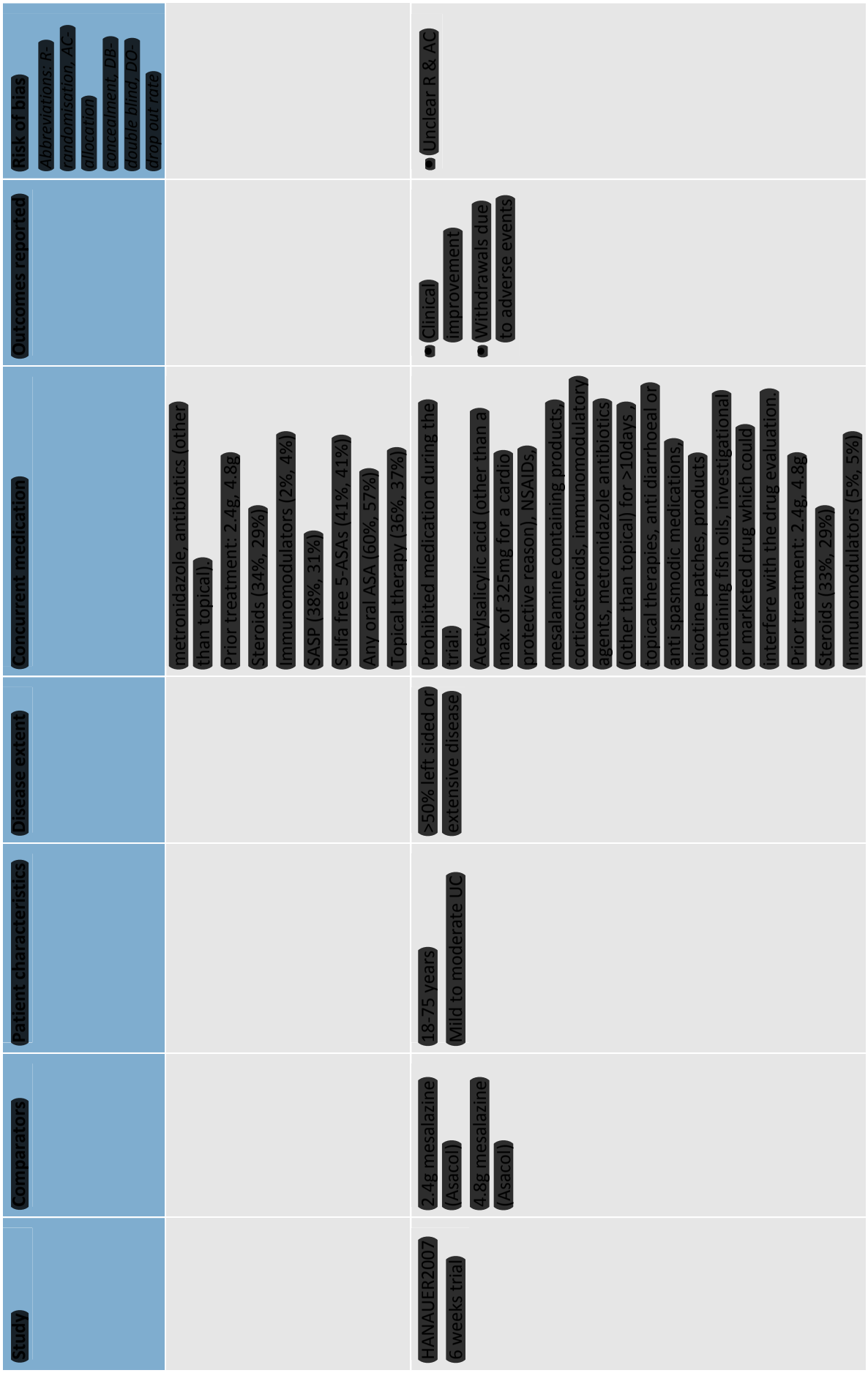
A total of 28 studies met the inclusion criteria and were included in one or more of the three networks. Table 2 below gives a summary of the characteristics of included studies.

Table 2: Baseline characteristics of included studies in the network meta-analysis

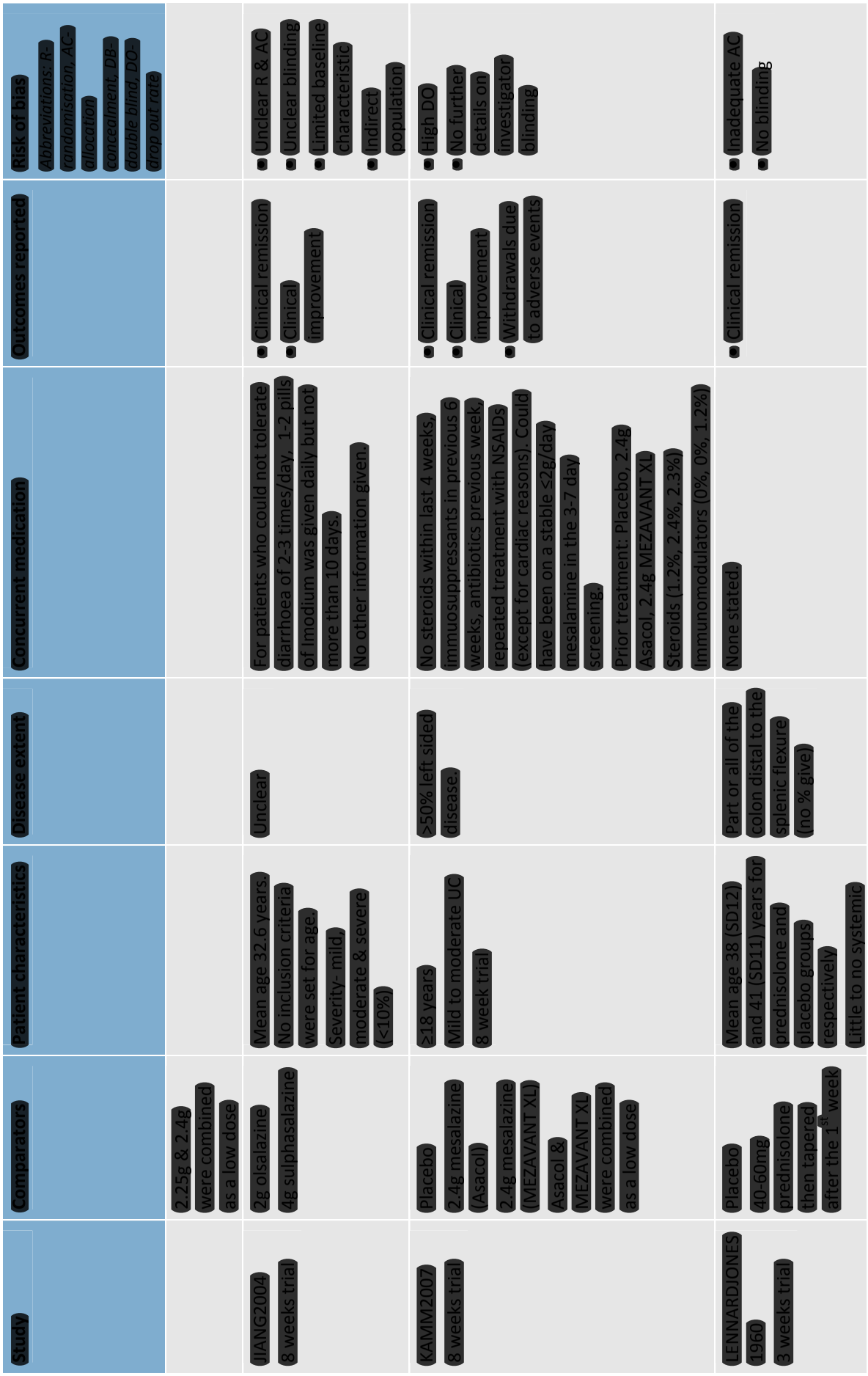
Study	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	Risk of bias *Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate*
CAMPIERI2003 4 weeks trial	2.4g mesalazine (Asacol) 5mg beclometasone	18-70 years Mild to moderate UC	All left sided or extensive disease	None allowed. Excluded if treated with a corticosteroid, 5-ASA or SASP for ≥1 month prior to enrolment.	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• Single blind • Differences at baseline (disease activity index and extent) • Beclometasone group more severe disease • >10% difference in missing data between the treatment arms
DICK1964 4 weeks trial	Placebo 4-6g sulphasalazine	Mild to moderate No age inclusion given	Split into colitis or proctitis. > 50% colitis, but unclear if that is left sided or extensive.	No SASP, corticosteroids or adrenocorticotrophins during the preceding three months. No further information given.	• Clinical improvement • Withdrawals due to adverse events	• Unclear R • Limited baseline characteristics • DB, no further information on physician blinding • Unclear accuracy of clinical assessment
FEURLE1989 4 weeks trial	Placebo 2g olsalazine	18-75 years Mild to moderate	Not described. Unclear.	None described. Excluded if patients were taking SASP, 5-ASA derivates, steroids, metronidazole.	• Withdrawals due to adverse events	• No baseline data on extent or severity

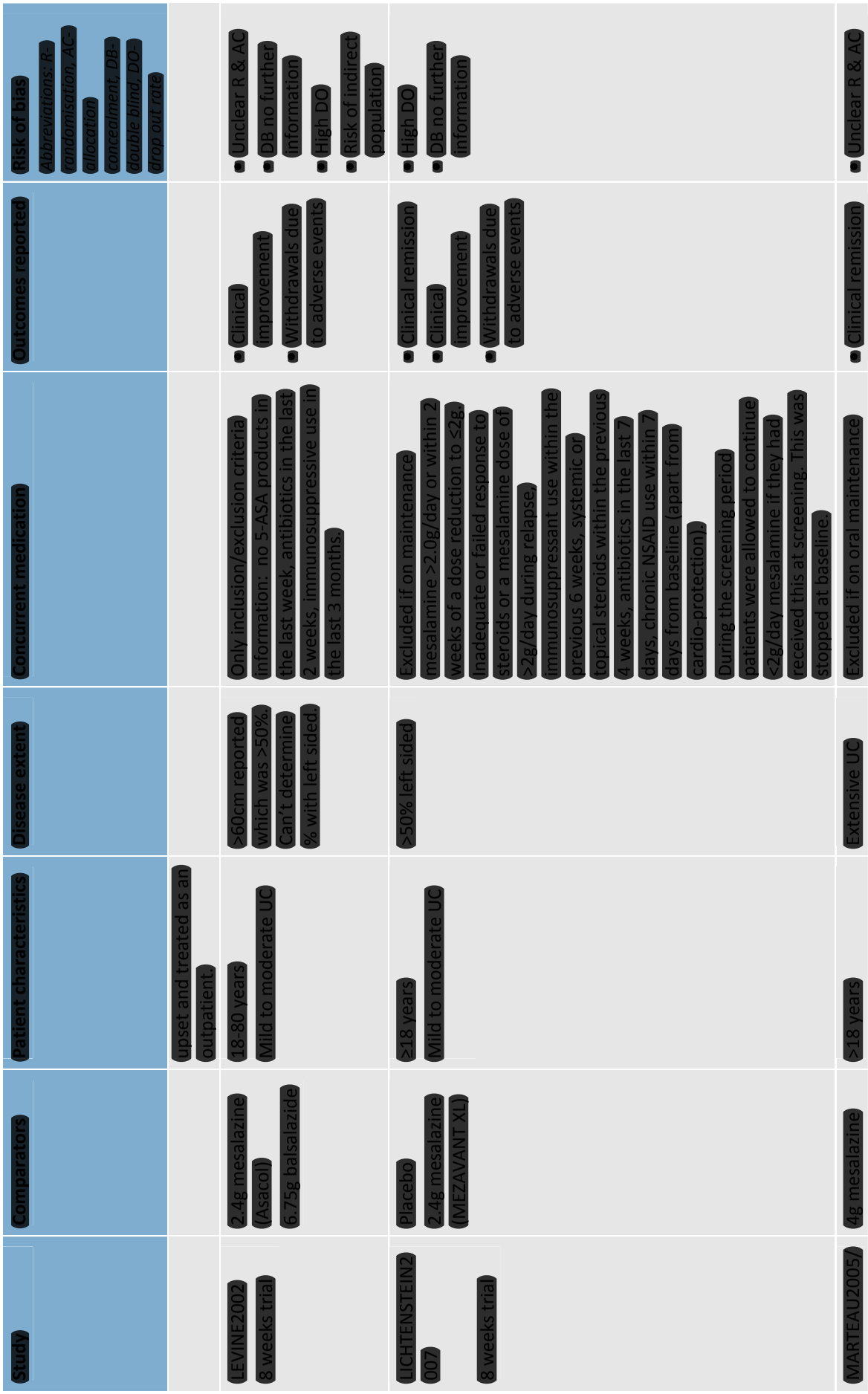

Study
Comparators
Patient characteristics
Disease extent
Concurrent medication
Outcomes reported
Risk of bias
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate
GREEN1998
12 weeks trial
2.4g mesalazine (unspecified)
6.75g balsalazide
18-80 years
Moderate or severe (but based on patients overall assessment not Truelove & Witts criteria)
≥12cm from anal margin.
All patients have left sided involvement of transverse colon or pancolitis.
azathioprine or similar drugs.
Topical steroid foam as relief medication for use as required (Colifoam).
Previous use of mesalazine or balsalazide in the last year was 10% and 4% respectively for both treatment groups.
Clinical remission
Withdrawals due to adverse events
Limited information on DB
Unclear R & AC
DB no further details
High DO
Risk of indirect population
HANAUER1993
8 weeks trial
Placebo
1g mesalazine (Pentasa) excluded
2g mesalazine (Pentasa)
4g mesalazine (Pentasa)
>18 years
Mild to moderate disease
All extents of disease. Unable to calculate % with left sided disease.
Not permitted to continue steroids, SASP, other mesalazine formulations (7 day washout), antispasmodics, antibiotics, NSAIDs and anti diarrhoeals (except Loperamide when absolutely necessary).
90 day immunomodulator washout.
Recent use of steroids for the placebo, 2g and 4g treatment groups was 28%, 21% and 29% respectively. For recent SASP use it was 42%, 41% and 40% respectively.
Clinical remission
Clinical improvement
Withdrawals due to adverse events
Unclear R & AC
DB no further information
High DO
HANAUER1996
12 weeks trial
Placebo
2g olsalazine
3g olsalazine
Mild to moderate disease
Abstract describes " no
Unknown – abstract.
No anti diarrhoeals allowed. No further information given.
Clinical remission
Withdrawals due to adverse events
Unclear R & AC
No baseline data as abstract

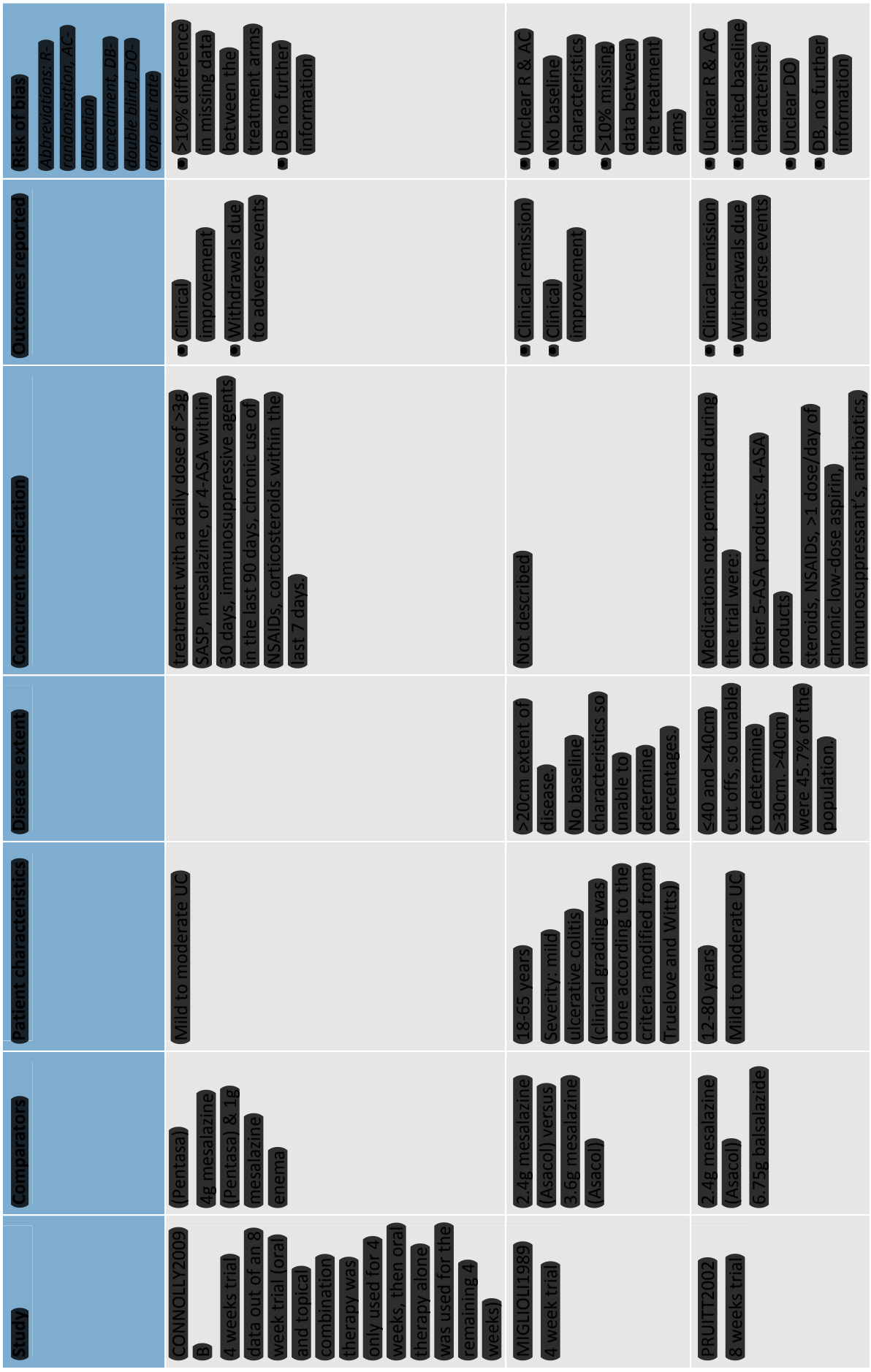

Risk of bias
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate
High DO
Extent unclear
Unclear R & AC
DB no further details
Outcomes reported
Clinical improvement
Withdrawals due to adverse events (moderate arms only)
Concurrent medication
None of the following drugs were permitted during the trial: Topical rectal therapies, anti-diarrhoeals and antispasmodics, immunomodulatory agents, nicotine patches, any products containing fish oils, or any investigational or marketed drug that may interfere with the evaluation of the study drug. And the following were also not permitted for longer than 10 days: Aspirin (apart for cardiac reasons), NSAIDs, mesalamine containing products, corticosteroids, sulphasalazine, 6-mercaptopurine, azathioprine, cyclosporine.
Disease extent
34% left sided, 20.5% pancolitis.
Patient characteristics
important differences in baseline demographics (age, gender and length of disease, duration of attack, endoscopy score and extent of disease, % newly diagnosed, stool/day and days with blood in stool."
18-75 years
Moderate UC
Comparators
Both doses were combined as a high dose
2.4g mesalazine (Asacol)
4.8g mesalazine (Asacol)
Mild and moderate severity groups for both of the above
Study
HANAUER2005
6 weeks trial


Study
Comparators
Patient characteristics
Disease extent
Concurrent medication
Outcomes reported
Risk of bias
HANAUER2007
6 weeks trial
2.4g mesalazine (Asacol)
4.8g mesalazine (Asacol)
18-75 years
Mild to moderate UC
≥50% left sided or extensive disease
metronidazole, antibiotics (other than topical)
Prior treatment: 2.4g, 4.8g
Steroids (34%, 29%)
Immunomodulators (2%, 4%)
SASP (38%, 31%)
Sulfa free 5-ASAs (41%, 41%)
Any oral ASA (60%, 57%)
Topical therapy (36%, 37%)
Prohibited medication during the trial:
Acetylsalicylic acid (other than a max. of 325mg for a cardio protective reason), NSAIDs, mesalamine containing products, corticosteroids, immunomodulatory agents, metronidazole antibiotics (other than topical) for >10days, topical therapies, anti diarrhoeal or anti spasmodic medications, nicotine patches, products containing fish oils, investigational or marketed drug which could interfere with the drug evaluation.
Prior treatment: 2.4g, 4.8g
Steroids (33%, 29%)
Immunomodulators (5%, 5%)
Clinical improvement
Withdrawals due to adverse events
Unclear R & AC
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate

Study	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	Risk of bias *Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate*
				SASP (37%, 29%) Sulfa free 5-ASAs (40%, 48%) Topical therapy (44%, 41%)		
HETZEL1986 6 weeks trial	Placebo 2g olsalazine	Mean age 45. No inclusion criteria given or SD. Mild to moderate	Left sided or proctitis. No % given.	Other therapy was ceased. Topical steroids or oral SASP but no other anti-diarrhoea medications were permitted up to 7 days prior to the start of the trial. Patients receiving oral steroids, azathioprine or other immunosuppressive, or antibiotics within 4 weeks of the trial were excluded.	• Clinical improvement • Withdrawals due to adverse events	• Unclear R & AC • High DO • No data on extent • DB no further information given • Unclear if validated clinical measure
HIWATASHI2011 8 week trial	2.25g mesalazine (Pentasa) versus 4g mesalazine (Pentasa)	15-64 years Severity: UCDAI score of 6-8 points, moderately active UC	All extents apart from proctitis. Reports all patients to have left sided or enterocolitis	None described. A washout period was needed prior to the trial for many of the drugs used in ulcerative colitis.	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• Unclear R & AC • >10% difference in missing data between treatment arms
ITO2010A 8 weeks trial	Placebo 2.25g mesalazine (Pentasa) 2.4g mesalazine (Asacol) 3.6g mesalazine (Asacol)	16-64 years Mild to moderate	All extents. Unable to calculate % with left sided disease.	Following participants were excluded: Mesalamine >2.25g/day or enemas, salazosulfapyridine >4.5g/day or suppositories, corticosteroids, cytapheresis within the last 14 days.	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• High DO

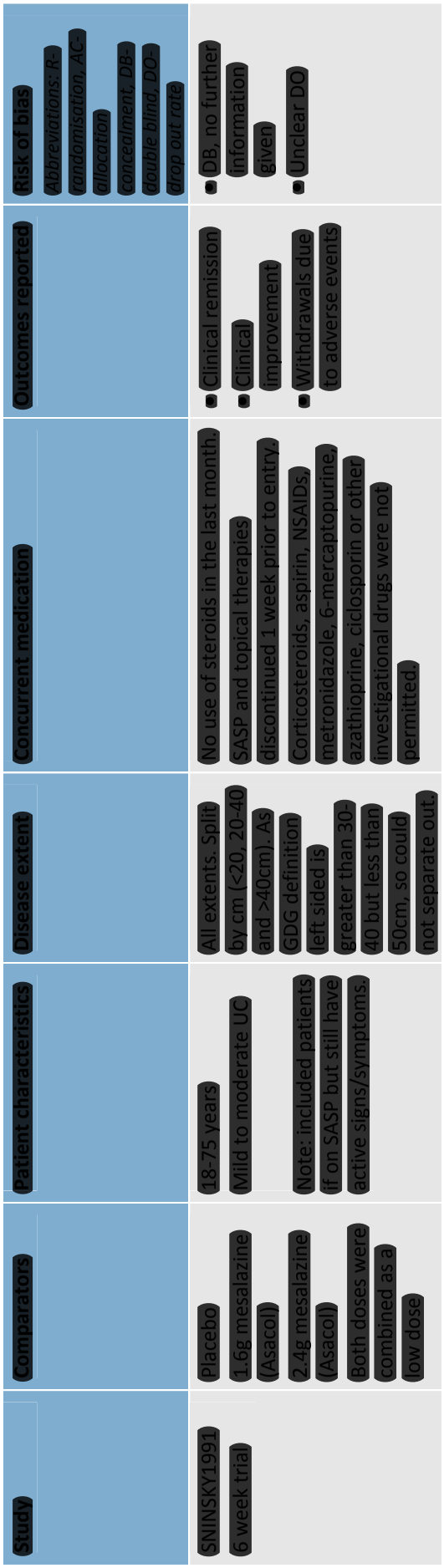

Study
Comparators
Patient characteristics
Disease extent
Concurrent medication
Outcomes reported
Risk of bias
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate
JIANG2004
8 weeks trial
2.25g & 2.4g were combined as a low dose
2g olsalazine
4g sulphasalazine
Mean age 32.6 years.
No inclusion criteria were set for age.
Severity- mild, moderate & severe (<10%)
Unclear
For patients who could not tolerate diarrhoea of 2-3 times/day, 1-2 pills of Imodium was given daily but not more than 10 days.
No other information given.
Clinical remission
Clinical improvement
Unclear R & AC
Unclear blinding
Limited baseline characteristic
Indirect population
KAMM2007
8 weeks trial
Placebo
2.4g mesalazine (Asacol)
2.4g mesalazine (MEZAVANT XL)
Asacol & MEZAVANT XL were combined as a low dose
≥18 years
Mild to moderate UC
8 week trial
>50% left sided disease.
No steroids within last 4 weeks, immuosuppressants in previous 6 weeks, antibiotics previous week, repeated treatment with NSAIDs (except for cardiac reasons). Could have been on a stable ≤2g/day mesalamine in the 3-7 day screening.
Prior treatment: Placebo, 2.4g Asacol, 2.4g MEZAVANT XL
Steroids (1.2%, 2.4%, 2.3%)
Immunomodulators (0%, 0%, 1.2%)
Clinical remission
Clinical improvement
Withdrawals due to adverse events
High DO
No further details on investigator blinding
LENNARDJONES
1960
3 weeks trial
Placebo
40-60mg prednisolone then tapered after the 1st week
Mean age 38 (SD12) and 41 (SD11) years for prednisolone and placebo groups respectively
Little to no systemic
Part or all of the colon distal to the splenic flexure (no % give)
None stated.
Clinical remission
Inadequate AC
No blinding


Study
Comparators
Patient characteristics
Disease extent
Concurrent medication
Outcomes reported
Risk of bias
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate
LEVINE2002
8 weeks trial
2.4g mesalazine (Asacol)
6.75g balsalazide
upset and treated as an outpatient.
18-80 years
Mild to moderate UC
≥60cm reported which was >50%. Can't determine % with left sided.
Only inclusion/exclusion criteria information: no 5-ASA products in the last week, antibiotics in the last 2 weeks, immunosuppressive use in the last 3 months.
Clinical improvement
Withdrawals due to adverse events
Unclear R & AC
DB no further information
High DO
Risk of indirect population
LICHTENSTEIN2007
8 weeks trial
Placebo
2.4g mesalazine (MEZAVANT XL)
≥18 years
Mild to moderate UC
>50% left sided
Excluded if on maintenance mesalamine >2.0g/day or within 2 weeks of a dose reduction to ≤2g, inadequate or failed response to steroids or a mesalamine dose of >2g/day during relapse, immunosuppressant use within the previous 6 weeks, systemic or topical steroids within the previous 4 weeks, antibiotics in the last 7 days, chronic NSAID use within 7 days from baseline (apart from cardio-protection), During the screening period patients were allowed to continue <2g/day mesalamine if they had received this at screening. This was stopped at baseline.
Clinical remission
Clinical improvement
Withdrawals due to adverse events
High DO
DB no further information
MARTEAU2005
4g mesalazine
≥18 years
Extensive UC
Excluded if on oral maintenance
Clinical remission
Unclear R & AC


Study
Comparators
Patient characteristics
Disease extent
Concurrent medication
Outcomes reported
Risk of bias
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate
CONNOLLY2009 B
4 weeks trial data out of an 8 week trial (oral and topical combination therapy was only used for 4 weeks, then oral therapy alone was used for the remaining 4 weeks)
(Pentasa)
4g mesalazine
(Pentasa) & 1g mesalazine enema
Mild to moderate UC
treatment with a daily dose of >3g SASP, mesalazine, or 4-ASA within 30 days, immunosuppressive agents in the last 90 days, chronic use of NSAIDs, corticosteroids within the last 7 days.
(Clinical improvement
Withdrawals due to adverse events
≥10% difference in missing data between the treatment arms
DB no further information)
MIGLIOLI1989
4 week trial
2.4g mesalazine (Asacol) versus 3.6g mesalazine (Asacol)
18-65 years
Severity: mild ulcerative colitis (clinical grading was done according to the criteria modified from Truelove and Witts)
>20cm extent of disease.
No baseline characteristics so unable to determine percentages.
Not described
(Clinical remission
Clinical improvement
Unclear R & AC
No baseline characteristics
≥10% missing data between the treatment arms)
PRUITT2002
8 weeks trial
2.4g mesalazine (Asacol) 6.75g balsalazide
12-80 years
Mild to moderate UC
≤40 and >40cm cut offs, so unable to determine ≥30cm. >40cm were 45.7% of the population.
Medications not permitted during the trial were: Other 5-ASA products, 4-ASA products steroids, NSAIDs, >1 dose/day of chronic low-dose aspirin, immunosuppressant's, antibiotics,
(Clinical remission
Withdrawals due to adverse events
Unclear R & AC
Limited baseline characteristic
Unclear DO
DB, no further information)

Study	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	Risk of bias *Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate*
				laxatives, anti-diarrhoeals, opiates, bile acid binders, topical rectal therapies.		given
RIZZELLO2002 4 week trial	3.2g mesalazine (Asacol) 3.2g mesalazine (Asacol) & 5mg beclometasone	≥18 years Mild to moderately severe UC	All extensive or left sided	None allowed. Excluded if had steroid treatment in month prior to study, 5-ASA>3.2g/day or SASP >2g/day for 2 weeks prior to study	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• Difference in proportions missing between groups is >10%
ROBINSON1988 4 week trial	Placebo 3g olsalazine	Data taken from the Cochrane review. No patient characteristics given in the abstract.	No extent data given in the abstract. Unclear.	No concurrent medications for UC were permitted.	• Clinical improvement • Withdrawals due to adverse events	• All methods were unclear (R, AC, baseline characteristics) • High DO • Unclear scoring of outcomes
SANDBORN2009 (A) 6 week trial	2.4g mesalazine (Asacol) 4.8g mesalazine (Asacol)	18-75 years Moderate UC	>50% left sided or extensive disease	Prohibited from taking: aspirin (for non cardio-protective reasons, max 325mg/day), NSAIDs, 5-ASA containing compounds, corticosteroids, immunomodulatory drugs, metronidazole, antibiotics (apart from topical) for >10 days throughout the study, antidiarrheal and/or antispasmodics, omega-3 fatty acid products, investigational or marketed drug that might	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	None.

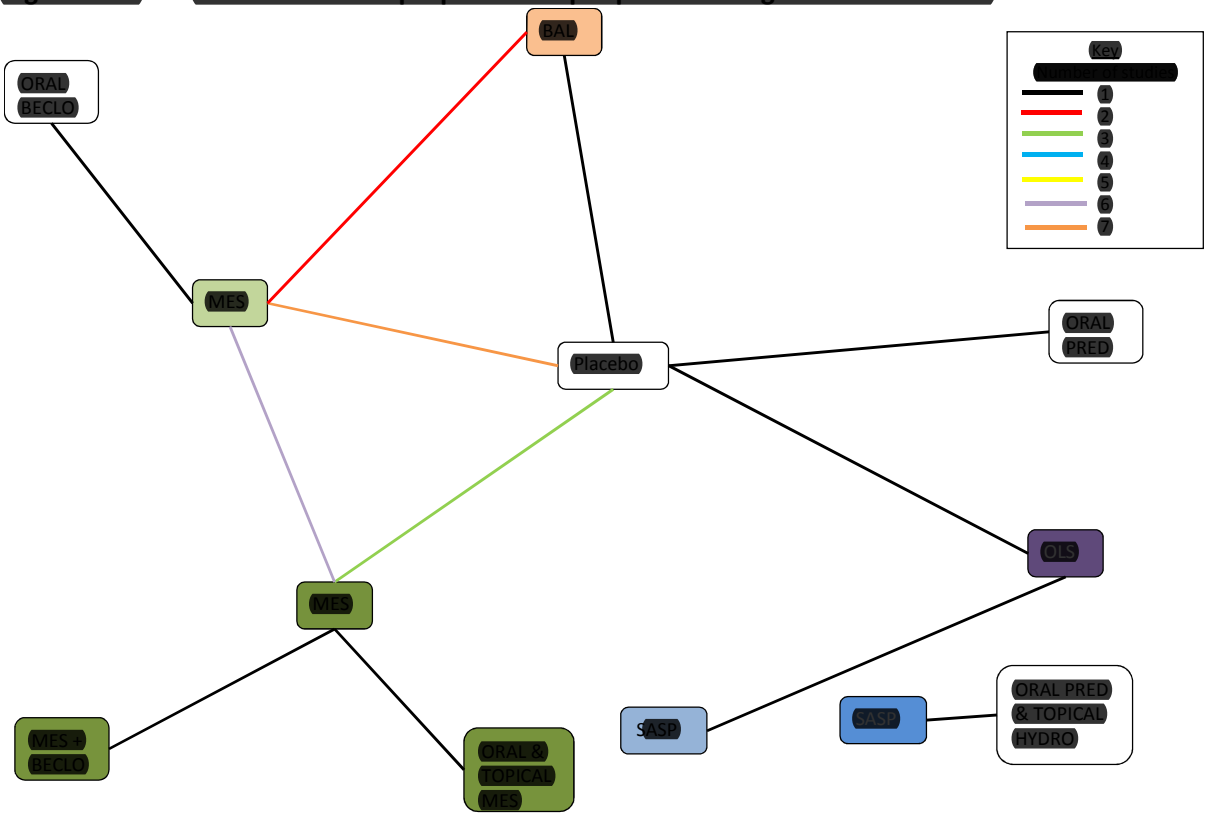
Study	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	Risk of bias *Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate*
				Interfere with the drug evaluation.		
SANDBORN2012 (B) 8 week trial	2.4g mesalazine (Asacol) versus placebo	Adults up to 75 years Severity: active mild to moderate ulcerative colitis for at least 6 months, UCDAI score of 4-10 points	Not proctitis. >50% left sided or extensive disease.	Not permitted. Other drugs used in ulcerative colitis were not allowed in the weeks prior to screening (different lengths for different drugs).	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• >10% difference in missing data between the treatment arms
SCHERL2009 8 week trial	Placebo 6.6g balsalazide	≥ 18 years Mild to moderate UC	≥20cm from the rectum. No % given.	Not described. Excluded if taken ≥6.75g balsalazide or >2.4g mesalamine or equivalent in the 2 weeks prior to the trial, chronic immunosuppressive therapy or corticosteroids within 30 days of screening, topical ASAs for >2 consecutive days during screening.	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• High DO • No baseline extent data
SCHROEDER1987 6 week trial	Placebo 1.6g mesalazine (Asacol) 4.8g mesalazine (Asacol)	Adults Mild to moderate UC	>50% left sided disease	No steroids or SASP within the last week or during the trial. Any other drugs for colitis were also prohibited in the trial.	• Clinical remission • Clinical improvement • Withdrawals due to adverse events	• Unclear AC • DB but no further information • High DO
SELBY1985 2 week trial	Placebo 2g olsalazine	15-81 years Mild UC	All left sided disease	If on SASP this was stopped at entry to the trial. Excluded patients on steroids or immunosuppressive drugs. 65% of those in the olsalazine groups took SASP prior to entry, and 60% in the placebo group.	• Clinical improvement	• Unclear R, AC & blinding


Study
Comparators
Patient characteristics
Disease extent
Concurrent medication
Outcomes reported
Risk of bias
SNINSKY1991
6 week trial
Placebo
1.6g mesalazine (Asacol)
2.4g mesalazine (Asacol)
Both doses were combined as a low dose
18-75 years
Mild to moderate UC
Note: included patients if on SASP but still have active signs/symptoms.
All extents. Split by cm (<20, 20-40 and >40cm). As GDG definition left sided is greater than 30-40 but less than 50cm, so could not separate out.
No use of steroids in the last month
SASP and topical therapies discontinued 1 week prior to entry
Corticosteroids, aspirin, NSAIDs, metronidazole, 6-mercaptopurine, azathioprine, ciclosporin or other investigational drugs were not permitted
Clinical remission
Clinical improvement
Withdrawals due to adverse events
DB, no further information given
Unclear DO
Abbreviations: R-randomisation, AC-allocation concealment, DB-double blind, DO-drop out rate

2.3.1 Network 1: Clinical remission

A total of 20 studies[12,20,43,46,49,57,60,62,65,81,83,88,90,109,115,121-124,126] from the original evidence review met the inclusion criteria and reported clinical remission. One study[130] which met the inclusion criteria but did not connect into the network was also excluded. Figure 278 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason(s) for exclusion on page 151.

Figure 278: Network for the proportion of people achieving clinical remission



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

MES-mesalazine, BAL – balsalazide, SASP- sulphasalazine, OLS- olsalazine, PRED – prednisolone, BUDES- budesonide, HYDRO- hydrocortisone, BECLO- beclometasone.

The majority of the trials were double blind apart from one which was single blind[12] and looked at oral beclometasone versus low dose mesalazine and one that was unblinded[81] comparing prednisolone to placebo. Eleven studies[19,43,46,49,57,62,81,88,90,109,124] had an unclear method of randomisation, allocation concealment or both. In nine studies[46,49,60,62,81,90,109,123,126], the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. When stated, the age for inclusion into the studies were mainly adults, ≥18 years, apart from three studies that included some young people with their inclusion criteria being 16-64years[57,60] and 12-80 years[109].

The trial data from the 20 studies included in the NMA for the proportion of people achieving clinical remission are presented in Table 3.

Table 3: Study data for the network of the proportion of people achieving clinical remission

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
CAMPIERI2003	Mesalazine-Asacol (2.4g)	Beclometasone (5mg)	N/A	50	87	46	90	N/A	N/A
GREEN1998	Mesalazine (2.4g)	Balsalazide (6.75g)	N/A	28	49	44	50	N/A	N/A
HANAUER1993	Placebo	Mesalazine-Pentasa (2g)	Mesalazine - Pentasa (4g)	11	90	28	97	28	95
HANAUER1996	Placebo	Olsalazine (2-3g)	N/A	12	90	27	183	N/A	N/A
ITO2010A	Placebo	Mesalazine-Asacol (2.4g) or Pentasa (2.25g)	Mesalazine - Asacol (3.6g)	3	33	38	131	29	65
HIWATASHI2011	Mesalazine-Pentasa (2.25g)	Mesalazine-Pentasa (4g)	N/A	9	63	13	60	N/A	N/A
JIANG2004	Olsalazine (2g)	Sulphasalazine (4g)	N/A	15	21	10	21	N/A	N/A
KAMM2007	Placebo	Mesalazine-Asacol & MEZAVANT XL (2.4g)	N/A	19	86	64	172	N/A	N/A
LENNARDJONES1960	Placebo (calcium lactate)	Prednisolone (40-60mg first week, then tapered)	N/A	3	18	9	19	N/A	N/A
LICHTENSTEIN2007	Placebo	Mesalazine – MEZAVANT XL (2.4g)	N/A	16	85	33	88	N/A	N/A
MARTEAU2005/ CONNOLLY2009B	Mesalazine (4g)	Mesalazine (4g) and topical mesalazine (1g) (Pentasa)	N/A	16	56	25	71	N/A	N/A
MIGLIOLI1989	Mesalazine-Asacol (2.4g)	Mesalazine-Asacol (3.6g)	N/A	9	24	11	24	N/A	N/A
PRUITT2002	Mesalazine-Asacol (2.4g)	Balsalazide (6.75g)	N/A	38	89	38	84	N/A	N/A
RIZZELLO2002	Mesalazine – Asacol (3.2g)	Mesalazine-Asacol (3.2g) & beclometasone (5mg)	N/A	21	61	34	58	N/A	N/A
SANDBORN2009A	Mesalazine - Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	121	383	152	389	N/A	N/A

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
SANDBORN2012B	Placebo	Mesalazine-Asacol (2.4g)	N/A	20	121	31	124	N/A	N/A
SCHERL2009	Placebo	Balsalazide (6.6g)	N/A	19	83	64	166	N/A	N/A
SCHROEDER1987	Placebo	Mesalazine-Asacol (1.6g)	Mesalazine - Asacol (4.8g)	2	38	1	11	9	38
SNINSKY1991	Placebo	Mesalazine-Asacol (1.6g or 2.4g)	N/A	2	52	12	106	N/A	N/A

A fixed and random effects model was run to determine which model is preferred which is indicated by a lower deviance information criteria (DIC). An important difference is classed as a DIC difference of 2-5. The fixed effects model DIC value was 248.395 and the random effects model DIC was 249.424. Therefore the fixed effects model was used for this baseline analysis.

Table 4 summarizes the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

Out of the treatments that were compared in the NMA, the combination of oral mesalazine and beclometasone, oral and topical mesalazine, balsalazide, prednisolone, high dose mesalazine and low dose mesalazine were found to be significantly better than placebo (Table 4). In addition, all of these treatments were also found to be significantly better than low dose sulphasalazine. High dose mesalazine was significantly better than low dose mesalazine and high dose olsalazine. The combination of mesalazine and beclometasone was also significantly better at inducing clinical remission compared to high dose olsalazine, high and low dose mesalazine, balsalazide and oral beclometasone alone.

High dose olsalazine is indicated to have no clinical difference compared to placebo, and be statistically significant lower clinical remission compared to high dose mesalazine, balsalazide and the two combination treatments.

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (44.14) closely matched the number of unconstrained data points (number of trial arms, n=41) indicating a goodness of fit for the model.

When the treatments were ranked in order of median relative risk (Figure 279) compared to placebo, the combination of oral mesalazine and beclometasone was the most highly ranked. It also had the highest probability of being the best treatment (67%).

However, due to the large overlapping confidence intervals of the different treatments, it is felt that there is insufficient evidence to be confident of one treatment's superiority compared to the

alternative treatment regimens for the induction of clinical remission in people with left sided or extensive ulcerative colitis compared to placebo.

Table 4: Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people in clinical remission at the end of the trial – Fixed effects

Placebo	**1.93 (1.51, 2.46)**	**3.21 (1.91, 5.39)**	1.11 (0.59, 2.08)	2.84 (0.91, 8.86)	**1.68 (1.09, 2.61)**				
1.84 (1.50, 2.24)	Low dose mesalazine	**1.27 (1.09, 1.48)**			**1.27 (1.02, 1.57)**	0.89 (0.68, 1.17)			
2.40 (1.90, 2.94)	**1.30 (1.12, 1.50)**	High dose mesalazine					**1.70 (1.13, 2.56)**	1.23 (0.73, 2.07)	
1.12 (0.60, 2.01)	0.61 (0.32, 1.13)	**0.47 (0.24, 0.87)**	High dose olsalazine						0.67 (0.39, 1.13)
3.09 (1.09, 5.45)	1.67 (0.59, 3.09)	1.29 (0.45, 2.40)	2.70 (0.85, 6.56)	Oral prednisolone					
2.31 (1.73, 3.00)	1.26 (0.95, 1.63)	0.97 (0.72, 1.29)	**2.06 (1.08, 4.06)**	0.75 (0.39, 2.17)	Balsalazide				
1.52 (0.89, 2.43)	0.83 (0.51, 1.26)	0.64 (0.38, 1.00)	1.36 (0.61, 2.94)	0.50 (0.22, 1.52)	0.66 (0.38, 1.09)	Oral beclometasone			
4.00 (2.69, 5.12)	**2.16 (1.49, 2.86)**	**1.66 (1.17, 2.17)**	**3.52 (1.77, 6.98)**	1.28 (0.64, 3.72)	**1.72 (1.12, 2.48)**	**2.60 (1.49, 4.63)**	Mesalazine & beclometasone		
2.88 (1.68, 4.23)	1.56 (0.94, 2.29)	1.20 (0.74, 1.74)	**2.54 (1.17, 5.39)**	0.93 (0.42, 2.79)	1.24 (0.71, 1.96)	1.88 (0.98, 3.54)	0.73 (0.42, 1.19)	Oral & topical mesalazine	
0.44 (0.10, 1.56)	**0.24 (0.05, 0.86)**	**0.18 (0.04, 0.67)**	0.39 (0.11, 1.19)	**0.15 (0.03, 0.72)**	**0.19 (0.04, 0.70)**	0.29 (0.06, 1.15)	**0.11 (0.02, 0.42)**	**0.15 (0.03, 0.60)**	Low dose SASP

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

Figure 279: Median relative risk ratio compared to placebo for treatments based on the outcome of clinical remission – Fixed effects

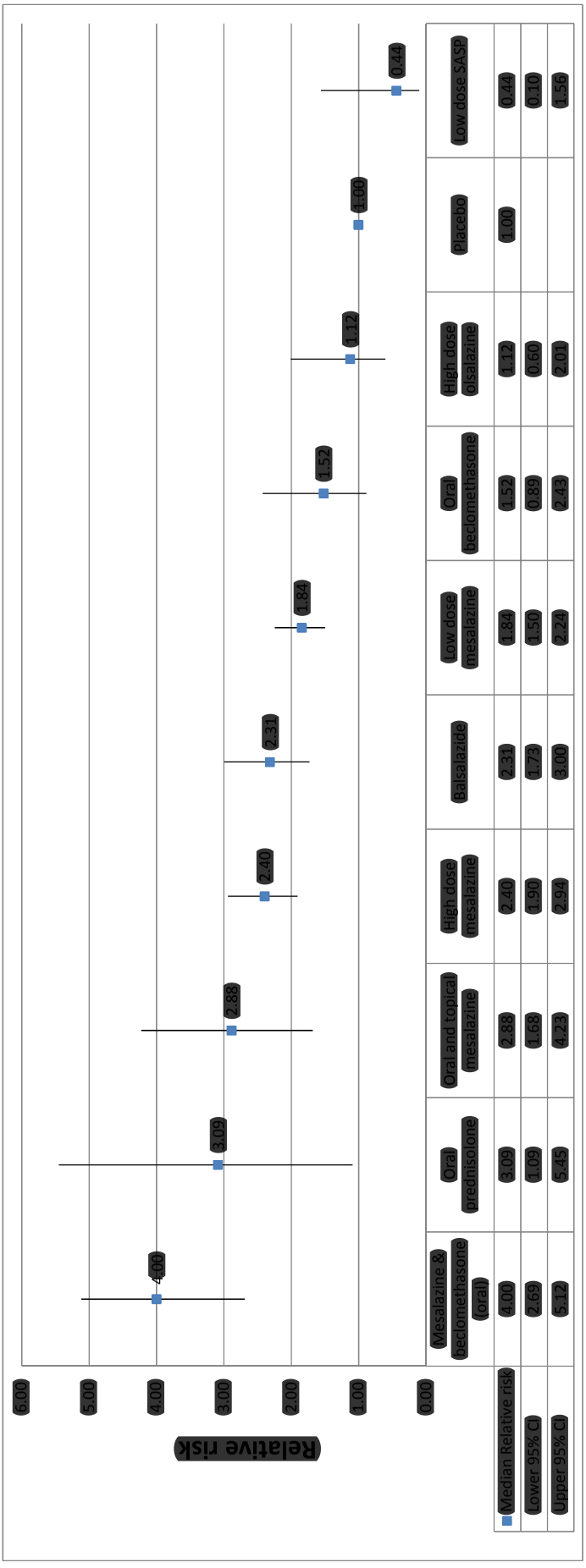


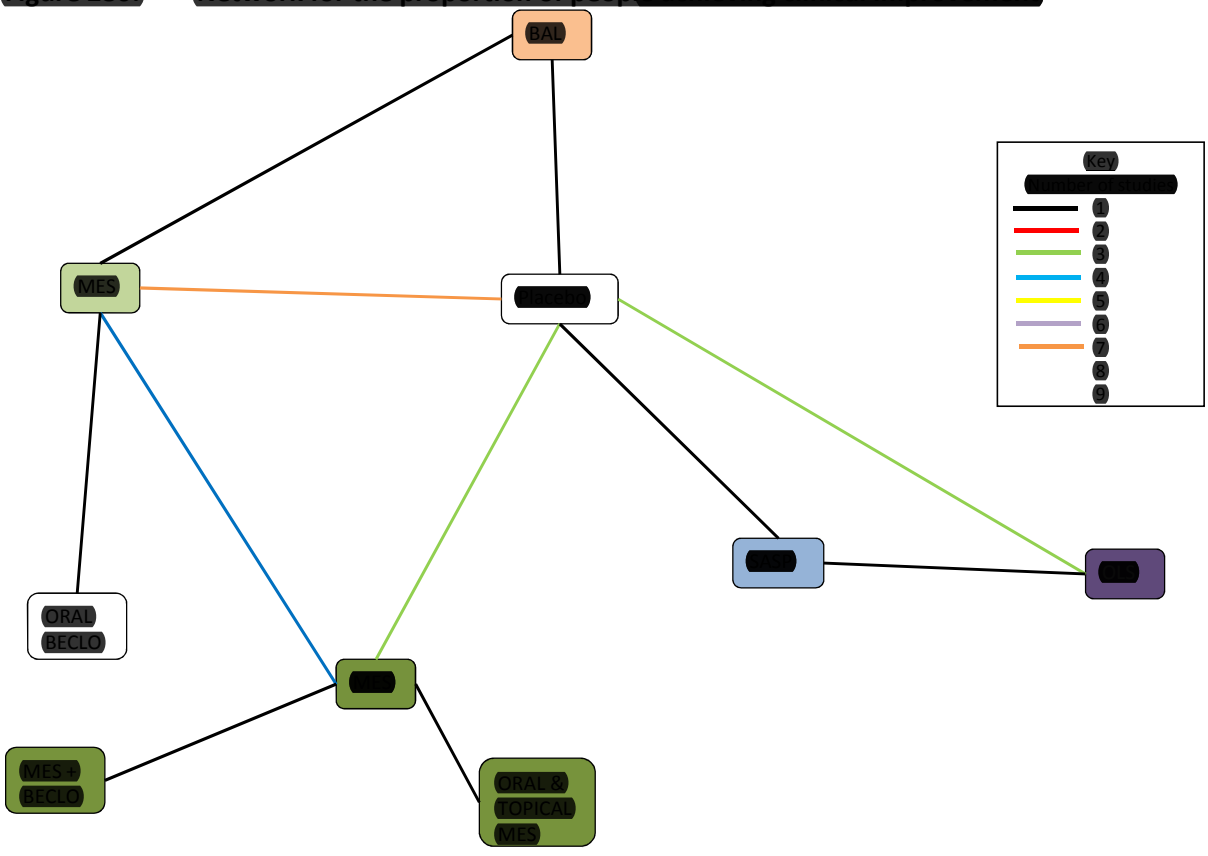
Table 5: The probability of each treatment being the best treatment for achieving clinical remission

Treatment	Probability of being the best treatment for achieving clinical remission – Fixed effects
Placebo	0%
Low dose mesalazine	0%
High dose mesalazine	0%
High dose olsalazine	0%
Oral prednisolone	26%
Balsalazide	0%
Oral beclometasone	0%
Mesalazine & beclometasone	67%
Oral & topical mesalazine	7%
Low dose sulphasalazine	0%

2.3.2 Network 2: Clinical improvement

A total of 23 studies[12,20,30,46,51,52,56,57,60,62,65,82,83,88,90,115,117,121-126] from the original evidence review met the inclusion criteria and reported clinical improvement. Figure 280 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason(s) for exclusion on page 151.

Figure 280: Network for the proportion of people achieving clinical improvement



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

(MES-mesalazine, BAL – balsalazide, SASP- sulphasalazine, OLS- olsalazine, PRED – prednisolone, BUDES- budesonide, HYDRO- hydrocortisone, BECLO- beclometasone.)

Most of the studies[20,30,46,51,52,56,57,60,65,82,83,88,90,115,117,121-124,126] were double blind, apart from two studies[62,125] where the blinding was not clear and one study[12] that was single blind.

Twelve studies had an unclear method of randomisation and allocation concealment[46,51,52,56,57,62,82,90,117,125], one study[19,88,124] had unclear allocation concealment another study[30] unclear randomisation. In ten studies[30,46,56,60,62,90,117,123,124,126], the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/ unclear inclusion criteria. When stated, all of the studies were an adult population apart from two studies[57,60] that also included some young people (16-64, 15-64 years).

The trial data from the 23 studies included in the NMA for the proportion of people achieving clinical improvement are presented in Table 6.

Table 6: Study data for the network of the proportion of people achieving clinical improvement

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
CAMPIERI2003	Mesalazine-Asacol (2.4g)	Beclometasone (5mg)	N/A	59	87	57	90	N/A	N/A
DICK1964	Placebo	Sulphasalazine (4-6g)	N/A	9	23	14	21	N/A	N/A
HANAUER1993	Placebo	Mesalazine-Pentasa (2g)	Mesalazine-Pentasa (4g)	49	90	77	97	80	95
HANAUER2005mild	Mesalazine-Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	21	52	19	58	N/A	N/A
HANAUER2005moderate	Mesalazine-Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	77	139	89	129	N/A	N/A
HANAUER2007	Mesalazine-Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	77	150	76	136	N/A	N/A
HETZEL1986	Placebo	Olsalazine (2g)	N/A	2	15	6	15	N/A	N/A
HIWATASHI2011	Mesalazine-Pentasa (2.25g)	Mesalazine-Pentasa (4g)	N/A	27	63	45	60	N/A	N/A
ITO2010A	Placebo	Mesalazine-Asacol (2.4g) or Pentasa (2.25g)	Mesalazine-Asacol (3.6g)	9	33	61	131	41	65
JIANG2004	Olsalazine (2g)	Sulphasalazine (4g)	N/A	20	21	15	21	N/A	N/A
KAMM2007	Placebo	Mesalazine-Asacol & MEZAVANT XL (2.4g)	N/A	34	86	99	172	N/A	N/A

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
LEVINE2002	Balsalazide (6.75g)	Mesalazine-Asacol (2.4g)	N/A	22	53	22	51	N/A	N/A
LICHTENSTEIN2007	Placebo	Mesalazine – MEZAVANT XL (2.4g)	N/A	22	85	49	88	N/A	N/A
MARTEAU2005/ CONNOLLY2009B	Mesalazine (4g)	Mesalazine (4g) and topical mesalazine (1g) (Pentasa)	N/A	29	56	51	71		N/A
MIGLIOLI1989	Mesalazine – Asacol (2.4g)	Mesalazine – Asacol (3.6g)	N/A	11	24	18	24	N/A	N/A
ROBINSON1988	Placebo	Olsalazine (3g)	N/A	16	48	25	50	N/A	N/A
RIZZELLO2002	Mesalazine – Asacol (3.2g)	Mesalazine-Asacol (3.2g) & beclometasone (5mg)	N/A	31	61	44	58	N/A	N/A
SANDBORN2009A	Mesalazine - Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	251	383	273	389	N/A	N/A
SANDBORN2012B	Placebo	Mesalazine – Asacol (2.4g)	N/A	30	121	42	124	N/A	N/A
SCHERL2009	Placebo	Balsalazide (6.6g)	N/A	33	83	92	166	N/A	N/A
SCHROEDER1987	Placebo	Mesalazine-Asacol (1.6g)	Mesalazine-Asacol (4.8g)	7	38	3	11	28	38
SELBY1985	Placebo	Olsalazine (2g)	N/A	8	20	13	20	N/A	N/A
SNINSKY1991	Placebo	Mesalazine-Asacol (1.6g or 2.4g)	N/A	8	52	28	106	N/A	N/A

Table 7 summarises the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

A fixed and random effects model was run to determine which model is preferred which is indicated by lower deviance information criteria (DIC). An important difference is classed as a DIC difference of 2-5. The fixed effects model DIC value was 310.153 and the random effects model DIC was 306.416. Therefore the random effects model was used for this baseline analysis.

Out of the treatments that were compared in the NMA, all of the treatments apart from low dose sulphasalazine and oral beclometasone were significantly better than placebo for clinical improvement. The combination treatment of oral mesalazine and beclometasone was significantly better than all the other treatments that it was compared to for clinical improvement apart from the combination treatment of oral and topical mesalazine. Oral and topical mesalazine were significantly better than low dose mesalazine, low dose sulphasalazine, balsalazide and oral beclometasone. The higher dose of mesalazine was significantly better for clinical improvement than the lower dose.

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (51.86) closely matched the number of unconstrained data points (number of trial arms, n=49) indicating a goodness of fit for the model.

When the treatments were ranked in order of median relative risk (Table 8) compared to placebo, the combination of oral mesalazine and beclometasone had the highest ranking. It also had the highest probability of being the best treatment for clinical improvement (63%), followed second by the combination of an oral and topical mesalazine (36%). All the other treatments were ranked very low in achieving this outcome.

Table 7: Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people with clinical improvement at the end of the trial – random effects

Placebo	**1.54 (1.34, 1.77)**	**2.26 (1.25, 4.07)**	1.70 (0.94, 3.08)	**1.75 (1.19, 2.57)**	**1.39 (1.03, 1.88)**			
1.67 (1.40, 1.95)	Low dose mesalazine	**1.20 (1.06, 1.36)**			0.96 (0.61, 1.51)	0.93 (0.75, 1.16)		
2.07 (1.78, 2.38)	**1.24 (1.11, 1.43)**	High dose mesalazine					**1.49 (1.12, 1.99)**	**1.39 (1.04, 1.86)**
1.34 (0.58, 2.19)	0.80 (0.34, 1.35)	0.65 (0.28, 1.08)	Low dose SASP	1.33 (1.00, 1.78)				
1.86 (1.31, 2.38)	1.11 (0.76, 1.51)	0.90 (0.62, 1.19)	1.39 (0.81, 3.13)	High dose olsalazine				
1.53 (1.01, 2.06)	0.91 (0.61, 1.26)	0.74 (0.48, 1.01)	1.14 (0.60, 2.75)	0.82 (0.51, 1.30)	Balsalazide			
1.52 (0.79, 2.26)	0.91 (0.50, 1.33)	0.73 (0.39, 1.08)	1.13 (0.51, 2.86)	0.82 (0.41, 1.38)	0.99 (0.50, 1.74)	Oral beclometasone		
2.66 (2.07, 2.93)	**1.57 (1.24, 1.90)**	**1.27 (1.01, 1.48)**	**1.95 (1.15, 4.54)**	**1.41 (1.01, 2.06)**	**1.71 (1.20, 2.63)**	**1.72 (1.11, 3.31)**	Mesalazine & beclometasone	
2.55 (1.92, 2.89)	**1.51 (1.16, 1.85)**	1.22 (0.94, 1.44)	**1.88 (1.08, 4.41)**	1.36 (0.94, 2.00)	**1.65 (1.12, 2.55)**	**1.66 (1.06, 3.18)**	0.96 (0.73, 1.24)	Oral & topical mesalazine

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

Figure 281: Median relative risk ratio compared to placebo for treatments based on the outcome of clinical improvement- Random effects

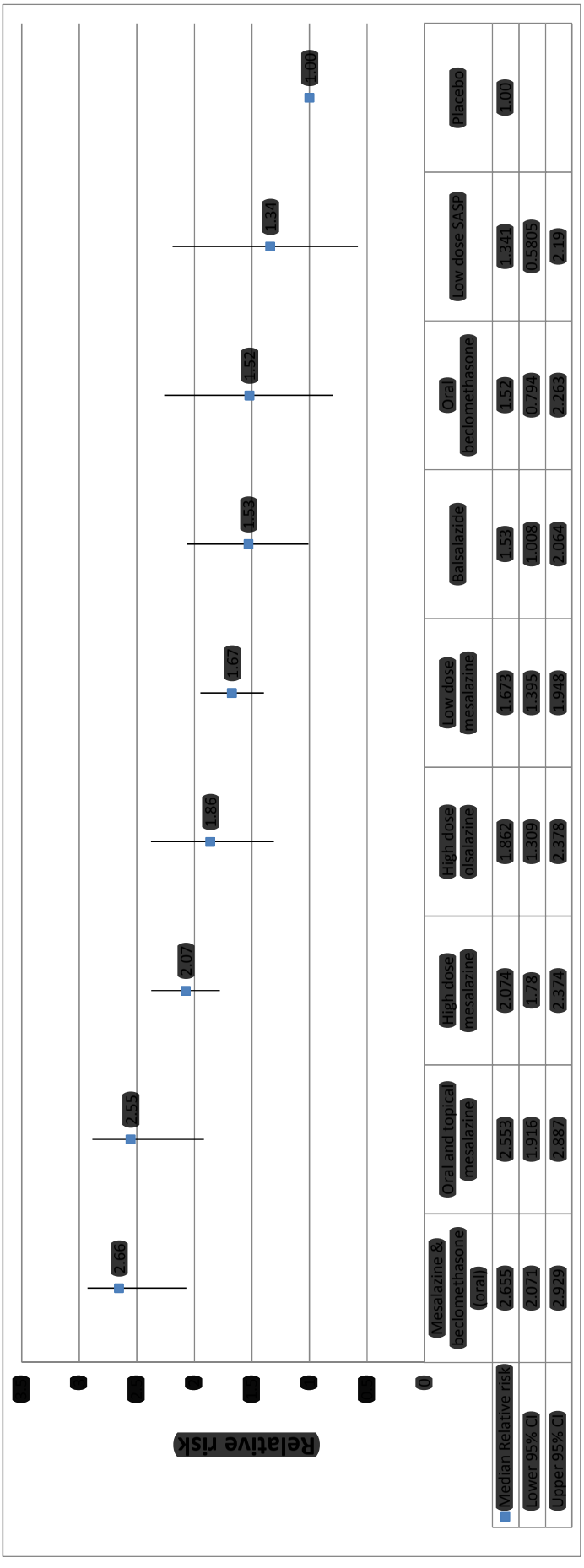


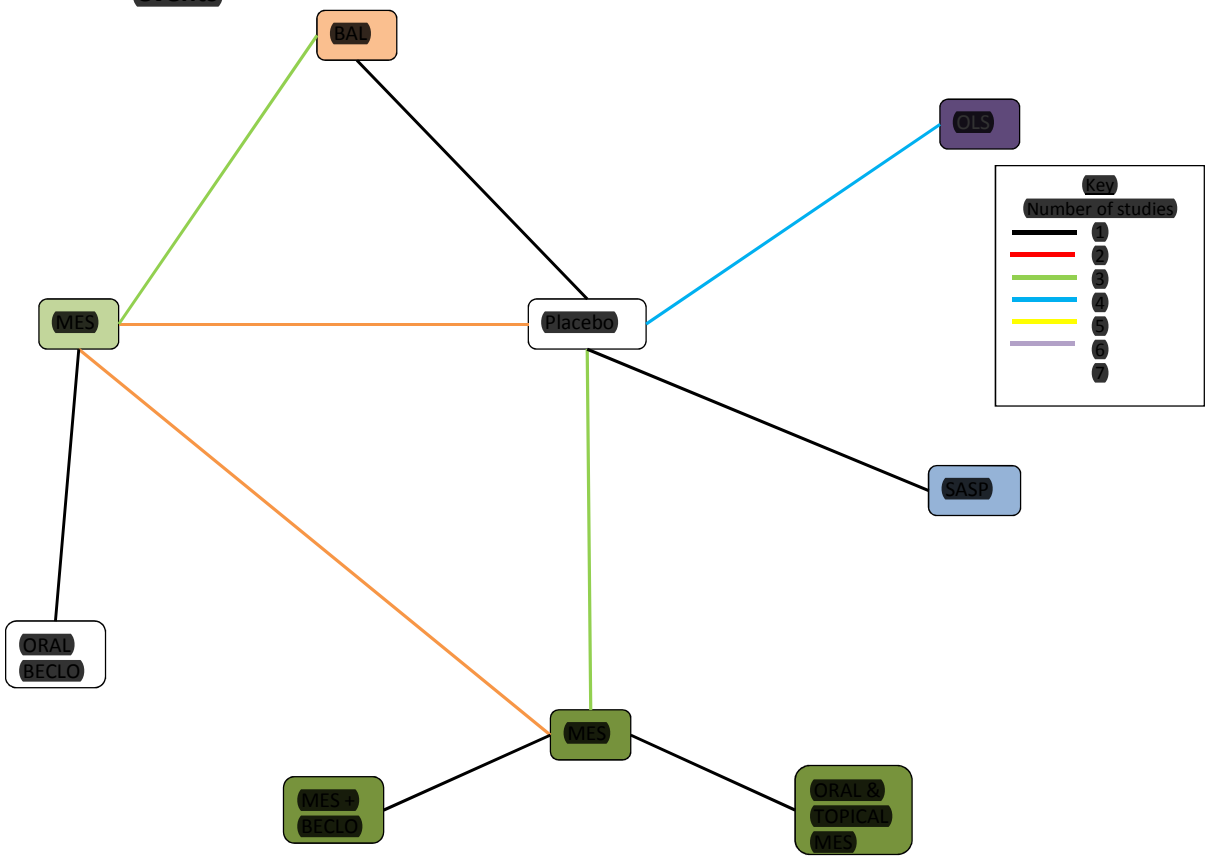
Table 8: The probability of each treatment being the best treatment for achieving clinical improvement

Treatment	Probability of being the best treatment for achieving clinical improvement – Random effects
Placebo	0%
Low dose mesalazine	0%
High dose mesalazine	0%
Low dose SASP	0%
High dose olsalazine	1%
Balsalazide	0%
Oral beclometasone	0%
Mesalazine & beclometasone (oral)	63%
Oral and topical mesalazine	36%

2.3.3 Network 3: Withdrawals due to adverse events

A total of 24 studies[12,20,30,37,43,46,49,51,52,56,57,60,65,82,83,88,109,115,117,121-124,126] from the original evidence review met the inclusion criteria and reported withdrawals due to adverse events. Figure 282 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason(s) for exclusion on page 151.

Figure 282: Network for the proportion of people withdrawing from treatment due to adverse events



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

MES-mesalazine, BAL – balsalazide, SASP- sulphasalazine, OLS- olsalazine, PRED – prednisolone, BUDES- budesonide, HYDRO- hydrocortisone, BECLO- beclometasone.

The studies[20,30,37,43,46,49,51,52,56,57,60,65,82,83,88,109,115,117,121-124,126] were all double blind apart from one study[12] that was single blind. Fourteen studies[19,30,43,46,49,51,52,56,57,82,88,109,117,124] had an unclear method of randomisation, allocation concealment or both. In 11 studies[30,37,43,46,49,56,60,109,117,123,126], the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. Three studies[57,60,109], included young people in their inclusion criteria, 16-64 years, 12-80 and 15-64 years.

The trial data from the 24 studies included in the NMA for the proportion of people withdrawing due to adverse events are presented in Table 9.

Table 9: Study data for the network of the proportion of people withdrawing due to adverse events

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
CAMPIERI2003	Mesalazine-Asacol (2.4g)	Beclometasone (5mg)	N/A	0*	87*	1*	90*	N/A	N/A
DICK1964	Placebo	Sulphasalazine (4-6g)	N/A	0*	23*	1*	21*	N/A	N/A
FEURLE1989	Placebo	Olsalazine (2g)	N/A	0*	53*	3*	52	N/A	N/A
GREEN1998	Mesalazine (2.4g)	Balsalazide (6.75g)	N/A	1	49	1	50	N/A	N/A
HANAUER1993	Placebo	Mesalazine-Pentasa (2g)	Mesalazine-Pentasa (4g)	11	90	9	97	7	95
HANAUER1996	Placebo	Olsalazine (2-3g)	N/A	2	90	17	183	N/A	N/A
HANAUER2005moderate	Mesalazine-Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	4	139	4	129	N/A	N/A
HANAUER2007	Mesalazine-Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	8	150	5	136	N/A	N/A
HETZEL1986	Placebo	Olsalazine (2g)	N/A	0*	15*	2*	15*	N/A	N/A
HIWATASHI2011	Mesalazine – Pentasa (2.25g)	Mesalazine – Pentasa (4g)	N/A	2*	63	0*	60	N/A	N/A
ITO2010A	Placebo	Mesalazine-Asacol (2.4g) or Pentasa (2.25g)	Mesalazine-Asacol (3.6g)	0*	33*	5*	131*	2*	65*
KAMM2007	Placebo	Mesalazine-Asacol & MEZAVANT	N/A	2	86	2	172	N/A	N/A

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
		XL (2.4g)							
LEVINE2002	Balsalazide (6.75g)	Mesalazine-Asacol (2.4g)	N/A	1	53	5	51	N/A	N/A
LICHTENSTEIN2007	Placebo	Mesalazine-MEZAVANT XL (2.4g)	N/A	11	85	5	88	N/A	N/A
MARTEAU2005/ CONNOLLY2009B	Mesalazine (4g)	Mesalazine (4g) and topical mesalazine (1g) (Pentasa)	N/A	6	56	9	71	N/A	N/A
PRUITT2002	Mesalazine-Asacol (2.4g)	Balsalazide (6.75g)	N/A	6	89	3	84	N/A	N/A
RIZZELLO2002	Mesalazine – Asacol (3.2g)	Mesalazine-Asacol (3.2g) & beclometasone (5mg)	N/A	3	61	1	58	N/A	N/A
ROBINSON1988	Placebo	Olsalazine (3g)	N/A	1	48	3	50	N/A	N/A
SANDBORN2009A	Mesalazine - Asacol (2.4g)	Mesalazine-Asacol (4.8g)	N/A	15	383	15	389	N/A	N/A
SANDBORN2012B	Placebo	Mesalazine-Asacol (3.6g)	N/A	10	121	7	124	N/A	N/A
SCHERL2009	Placebo	Balsalazide (6.6g)	N/A	10	83	15	166	N/A	N/A
SCHROEDER1987	Placebo	Mesalazine-Asacol (1.6g)	Mesalazine-Asacol (4.8g)	2	38	1	11	1	38
SNINSKY1991	Placebo	Mesalazine-Asacol (1.6g or 2.4g)	N/A	0*	52*	2*	106*	N/A	N/A

*(a) * due to one arm having zero events, one was added to all the numerators and denominators in the analysis*

Table 10 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

A fixed and random effects model was run to determine which model is preferred which is indicated by lower deviance information criteria (DIC). An important difference is classed as a DIC difference of 2-5. The fixed effects model DIC value was 217.852 and the random effects model DIC was 220.147. Therefore the fixed effects model was used for this baseline analysis.

Out of the treatments that were compared in the NMA, the only treatment to demonstrate a significant difference in withdrawals due to adverse event compared to placebo is high dose

olsalazine. There is also a significantly higher withdrawals with high dose olsalazine compared to low dose mesalazine, high dose mesalazine, balsalazide and both combination treatments (mesalazine and beclometasone, oral and topical mesalazine).

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (39.48) was close to the number of unconstrained data points (number of trial arms, n=45) indicating a goodness of fit for the model.

The probability of the treatment being the best (fewer withdrawals due to adverse events) was highest in oral mesalazine and beclometasone (75%) and balsalazide (12%).

Table 10: Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people who withdrew due to adverse events at the end of the trial – Fixed effect

Placebo	0.71 (0.44, 1.13)	0.67 (0.31, 1.46)	3.27 (0.37, 29.18)	**3.72 (1.43, 9.67)**	0.75 (0.35, 1.60)			
0.77 (0.50, 1.18)	Low dose mesalazine	0.84 (0.55, 1.28)			0.42 (0.15, 1.18)	1.93 (0.18, 20.95)		
0.65 (0.37, 1.10)	0.84 (0.55, 1.27)	High dose mesalazine					0.35 (0.04, 3.27)	1.18 (0.45, 3.13)
3.81 (0.48, 13.96)	4.92 (0.59, 19.91)	5.84 (0.69, 25.03)	Low dose SASP					
3.50 (1.61, 7.29)	**4.52 (1.87, 10.61)**	**5.38 (2.09, 13.48)**	0.92 (0.19, 8.29)	High dose olsalazine				
0.53 (0.27, 1.01)	0.68 (0.35, 1.33)	0.81 (0.38, 1.76)	0.14 (0.03, 1.21)	**0.15 (0.06, 0.41)**	Balsalazide			
1.73 (0.14, 12.36)	2.22 (0.19, 15.86)	2.65 (0.22, 19.72)	0.48 (0.03, 8.44)	0.50 (0.04, 4.12)	3.26 (0.25, 25.84)	Oral beclometasone		
0.18 (0.01, 1.65)	0.23 (0.01, 2.09)	0.27 (0.01, 2.39)	0.05 (0.00, 1.02)	**0.05 (0.00, 0.55)**	0.33 (0.01, 3.40)	0.10 (0.00, 2.85)	Mesalazine & beclometasone	
0.80 (0.24, 2.53)	1.03 (0.32, 3.17)	1.22 (0.42, 3.51)	0.21 (0.03, 2.27)	**0.23 (0.05, 0.92)**	1.50 (0.40, 5.49)	0.46 (0.05, 6.88)	4.58 (0.39, 155.30)	Oral & topical mesalazine

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

NOTE: If no events occurred in one treatment arm, one was added to the numerator and denominator of all arms. This was also done for the direct comparisons, to ensure consistency.

Figure 283: Median relative risk ratio compared to placebo for treatments based on the outcome of withdrawals due to adverse events – Fixed effects

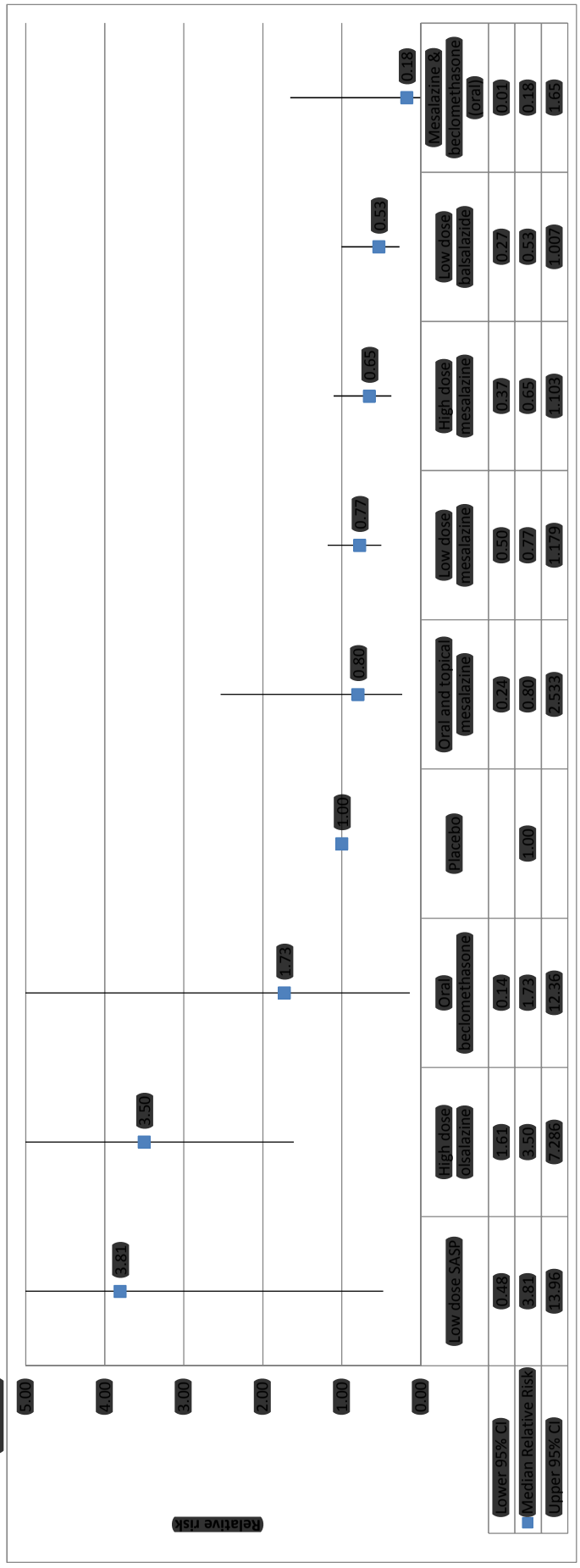


Table 11: The probability of each treatment being the best treatment for withdrawals due to adverse events

Treatment	Probability of being the best treatment for having the fewest withdrawals due to adverse events – Fixed effects
Placebo	0%
Low dose mesalazine	0%
High dose mesalazine	2%
Low dose SASP	1%
High dose olsalazine	0%
Balsalazide	12%
Oral beclometasone	6%
Mesalazine & beclometasone (oral)	75%
Oral and topical mesalazine	5%

2.3.4 Sensitivity analysis – Time points

A sensitivity analysis was carried out to look at the different time points at which the data from the trial was reported. Time until remission or clinical improvement was considered an important element in the induction of remission. Due to a lack of published hazard ratio data in the clinical review, the trial data was presented in relative risk ratios at the following time points;

- 0≤2 weeks
- >2 ≤4 weeks
- >4 ≤6 weeks
- >6 ≤8 weeks
- >8 weeks

In the baseline networks, the end of trial data was used. However, the GDG felt that it was important to determine whether the event rates differed at the four time intervals for the included treatments, and whether the ranking of their effectiveness changed. A sensitivity analysis was to be carried out looking at the networks for clinical remission and clinical improvement at the different time points. Some studies reported data at more than one time point within the trial. In this scenario there is no risk of double counting the data as they will be in different networks. This data has therefore been included.

The following figures illustrate the direct comparisons that were available for each time point and outcome:

Figure 284: Clinical remission (0≤2 weeks)

Figure 285: Clinical remission (>2 ≤4 weeks)

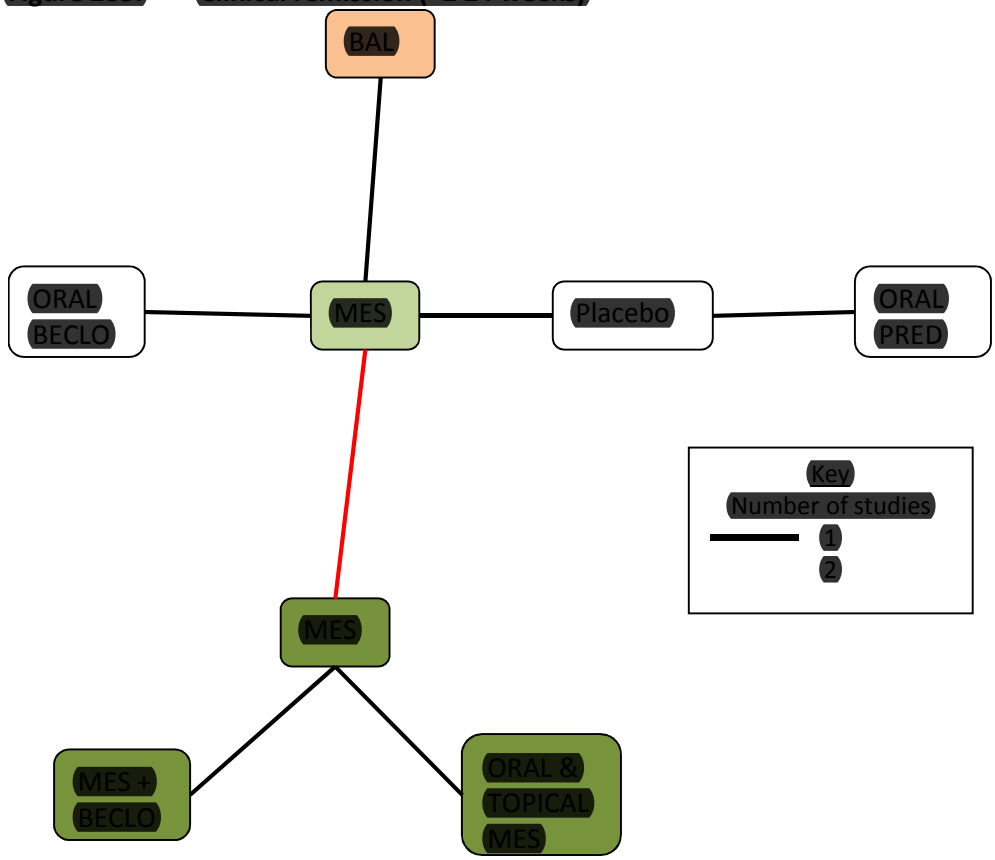


Figure 286: Clinical remission (>4 ≤6 weeks)

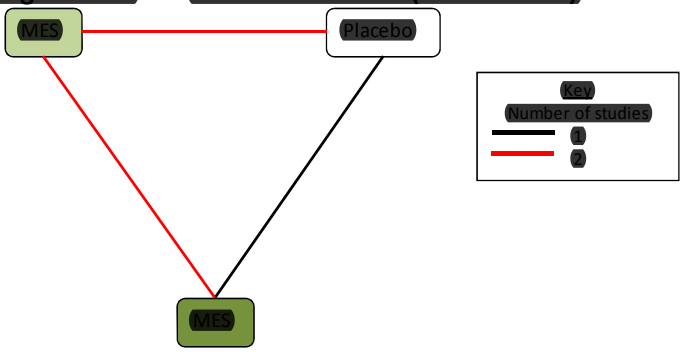


Figure 287: Clinical remission (>6 ≤8 weeks)

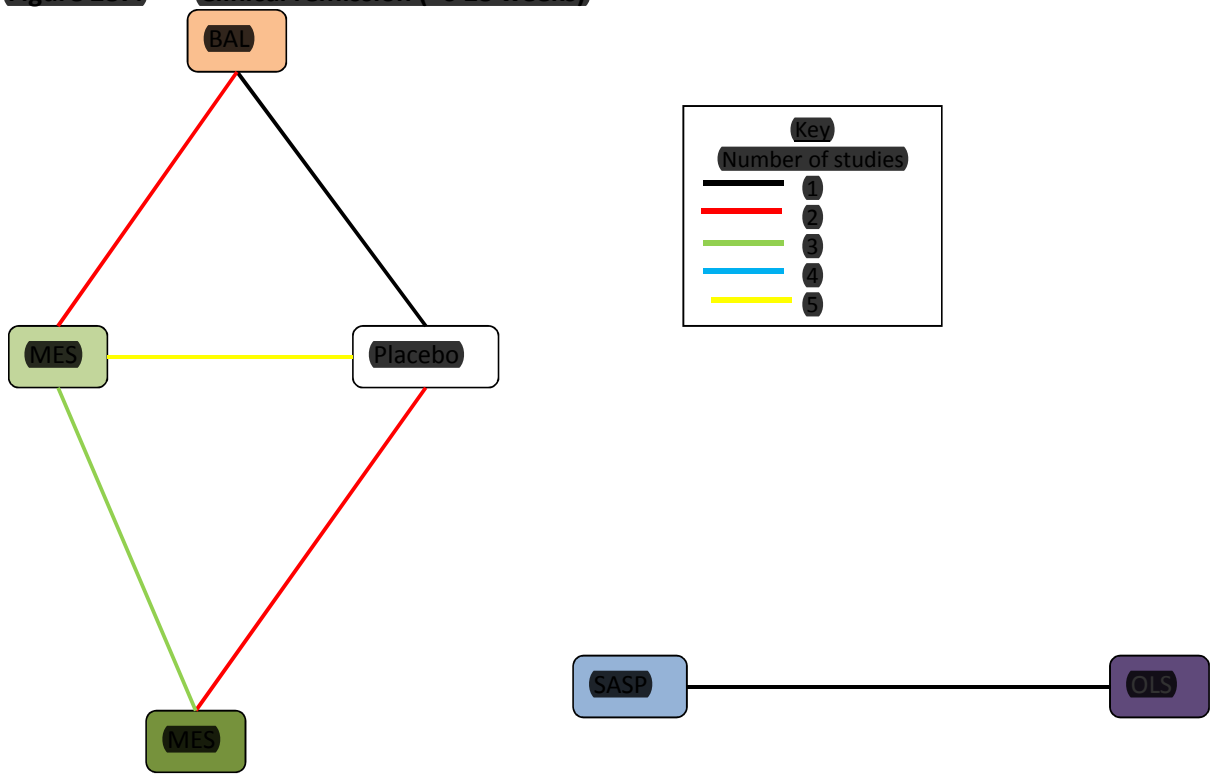


Figure 288: Clinical remission (>8 weeks)

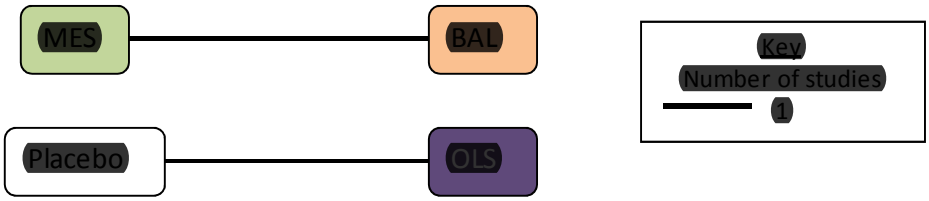


Figure 289: Clinical improvement (0 ≤2 weeks)

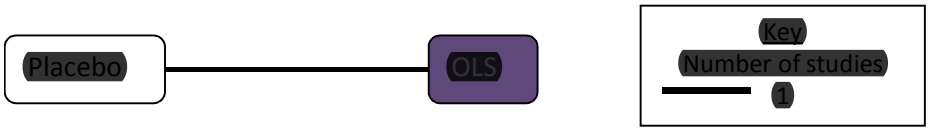


Figure 290: Clinical improvement (>2 ≤4 weeks)

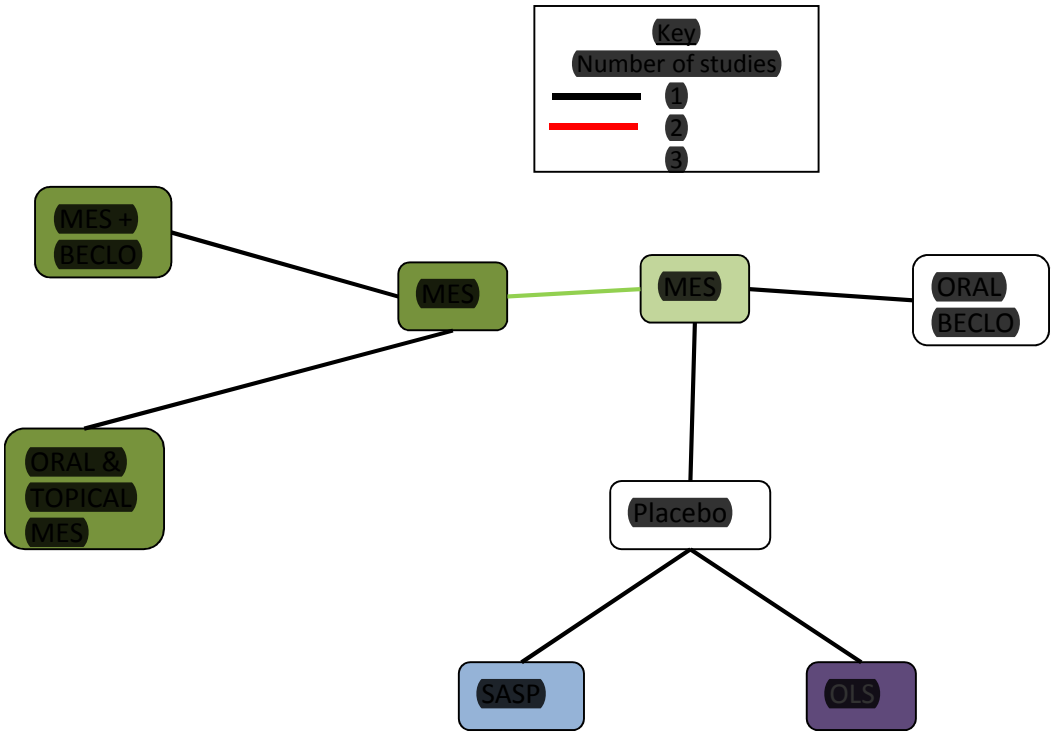


Figure 291: Clinical improvement (>4≤6 weeks)

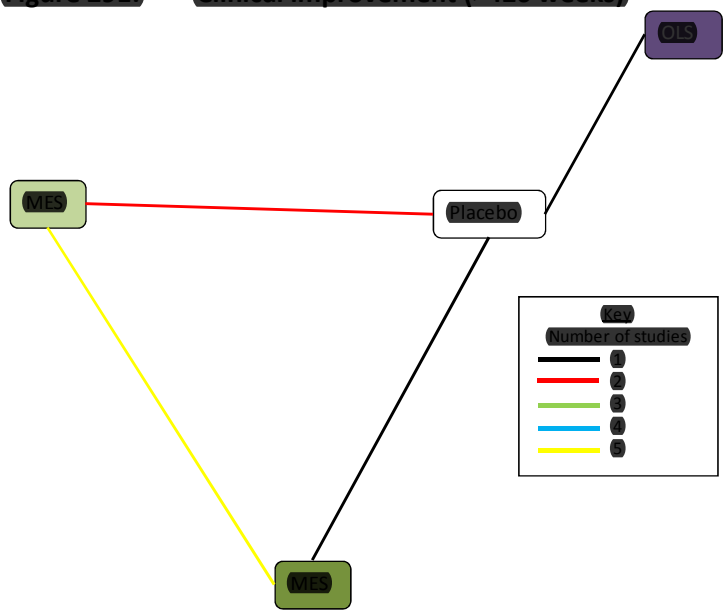
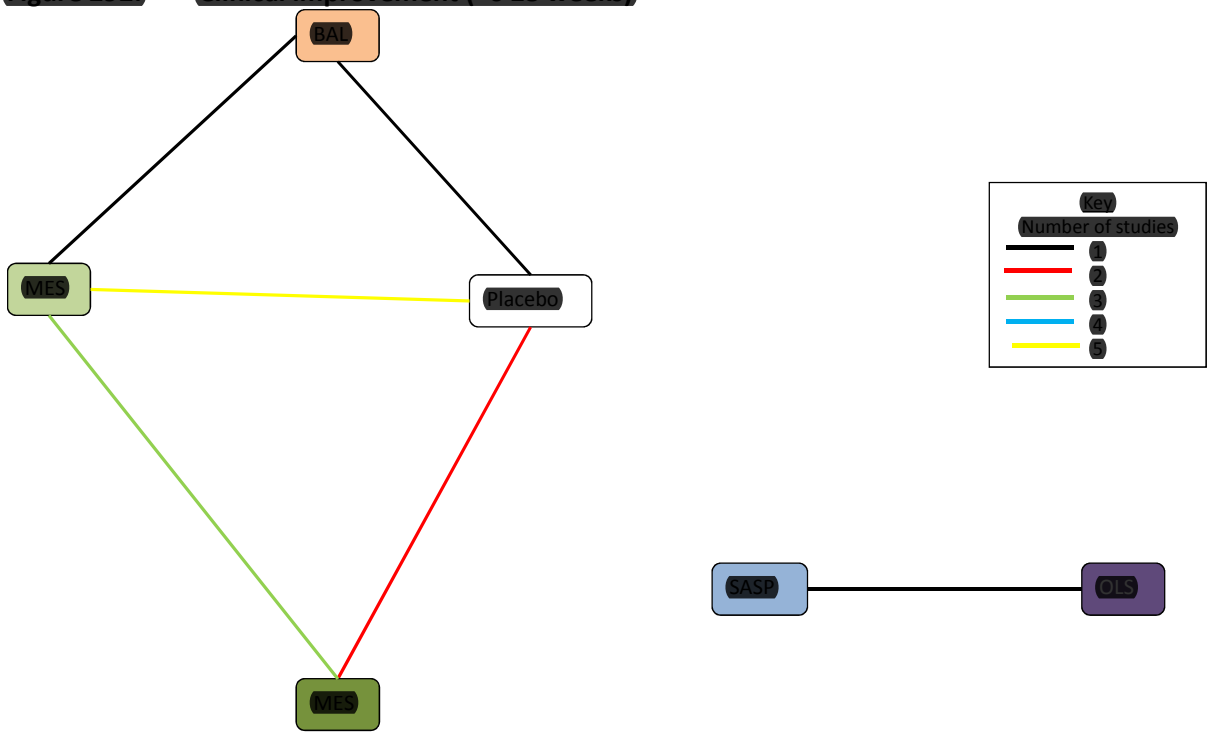


Figure 292: Clinical improvement (>6 ≤8 weeks)



2.3.5 Clinical remission

There were three networks which did not have a closed loop so therefore the NMA could not be internally validated, and was not carried out (0≤2, >2≤4 weeks, >8 weeks). The network for clinical remission at >4weeks ≤6 weeks would not provide very useful results as there were only two treatments (high and low dose mesalazine) that are connected together with a placebo group. The >6 weeks ≤8 weeks subgroup, would provide results on low, high dose mesalazine, balsalazide and placebo. The NMA was not run comparing the two subgroups (>4 ≤6 weeks, >6 weeks ≤8 weeks) because it would have only produced results comparing high and low dose mesalazine (balsalazide was only included for one time point) and placebo.

2.3.6 Clinical improvement

Similarly to the clinical remission networks, there were two networks which did not contain a closed loop (0≤2 weeks,>2≤4 weeks) and there was no data available at > 8weeks.

The other two time points had a closed loop but only had 4 treatments to compare (>4≤6 weeks and >6 ≤8 weeks respectively), only three of which could be compared across networks, low dose mesalazine, high dose mesalazine and placebo. The results of these would not be sufficient to impact the base case ranking of the NMA, so therefore the NMA scenario was not run.

2.4 Combined NMA results

A combined NMA was run following the results of the baseline analysis to look at the relationship between low and high dose aminosalicylates, beclometasone dipropionate and the combination treatments, oral mesalazine and oral beclometasone dipropionate, oral mesalazine and topical mesalazine. The analysis informed the inputs into the original health economic model.

From the baseline NMA results, high dose olsalazine was seen as an outlier. It was shown to have no statistically significant difference in clinical remission rates compared to placebo and low dose aminosalicylates (mesalazine and sulphasalazine) and had lower clinical remission rates compared to high dose alternative treatment options. It also had a statistically significant higher withdrawals due to adverse events rate compared to many of the other comparators. It was on this basis, that it was decided to be excluded from the combined NMA and health economic model.

The outcomes used in the health economic model consist of clinical remission and withdrawals due to adverse events, so for the combined NMA, clinical improvement was not analysed.

2.4.1 Network 1: Clinical remission

17 studies from the baseline NMA were included in the clinical remission combined network, with one study[62] being excluded due to one of its two comparators being high dose olsalazine.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots. A fixed effects model was run as per the baseline NMA.

Figure 293: Network for the proportion of people achieving clinical remission (combined NMA)

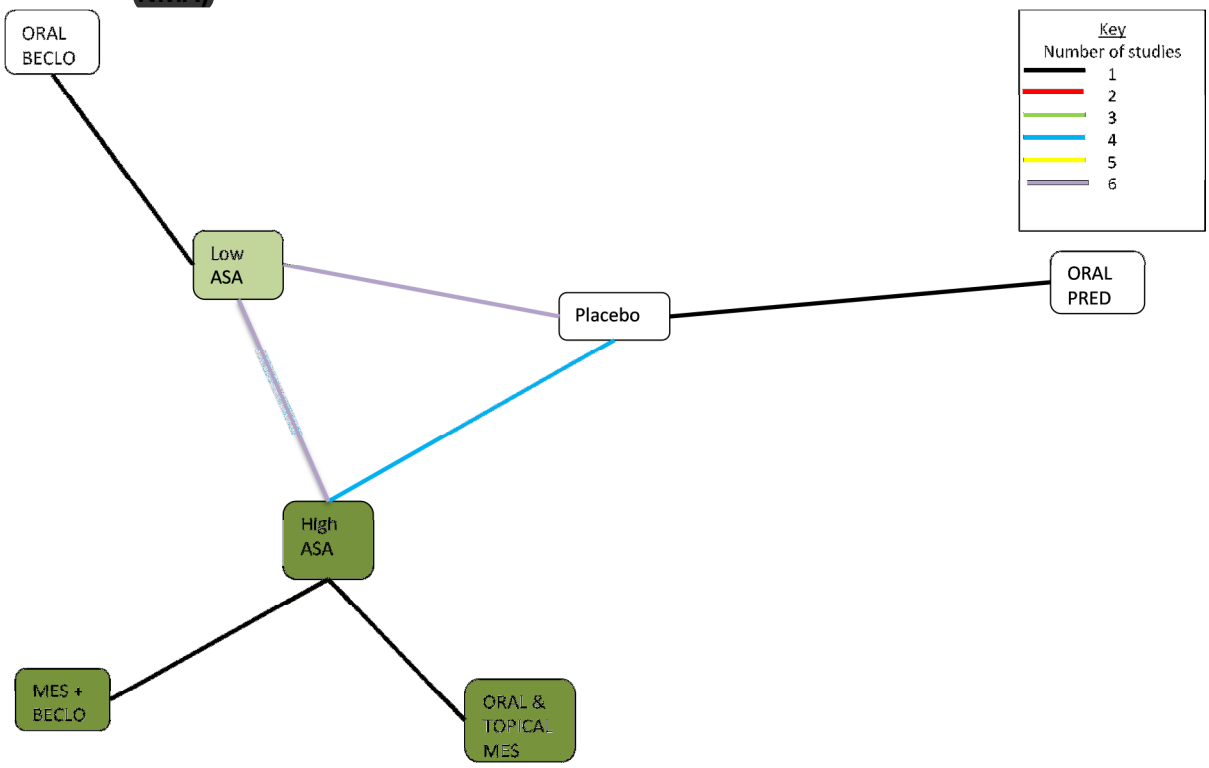


Table 12 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

Out of the treatments that were compared in the NMA, all of the treatments apart from oral beclometasone dipropionate had a significant difference in the proportion of people in clinical remission compared to placebo. The combination treatment of oral mesalazine and beclometasone

dipropionate was significantly better than low dose ASA, high dose ASA and oral beclometasone dipropionate alone. High dose oral ASA was significantly better than low dose oral ASA.

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (40.25) was close to the number of unconstrained data points (number of trial arms, n=37) indicating a goodness of fit for the model.

The probability of the treatment being the best (higher proportion of people in clinical remission) was highest in oral mesalazine and beclometasone (64%).

Table 14 shows the log odds ratios which are the inputs used for the health economic model.

Table 12. Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people in clinical remission at the end of the trial – Fixed effects

Placebo	1.93 (1.51, 2.46)	2.30 (1.65, 3.22)	2.84 (0.91, 8.86)				
1.79 (1.47, 2.16)	Low dose ASA	1.27 (1.12, 1.44)		0.89 (0.68, 1.17)			
2.29 (1.89, 2.74)	1.28 (1.12, 1.46)	High dose ASA			1.70 (1.13, 2.56)	1.23 (0.73, 2.07)	
2.99 (1.10, 5.10)	1.67 (0.61, 2.97)	1.30 (0.47, 2.31)	Oral prednisolone				
1.50 (0.88, 2.35)	0.84 (0.52, 1.27)	0.66 (0.40, 1.01)	0.51 (0.23, 1.50)	Oral beclometasone			
3.72 (2.54, 4.74)	2.07 (1.44, 2.72)	1.61 (1.14, 2.09)	1.24 (0.64, 3.48)	2.45 (1.43, 4.33)	Mesalazine & beclometasone		
2.75 (1.64, 3.95)	1.53 (0.94, 2.22)	1.20 (0.74, 1.70)	0.92 (0.43, 2.65)	1.82 (0.96, 3.39)	0.74 (0.43, 1.21)	Oral & topical mesalazine	

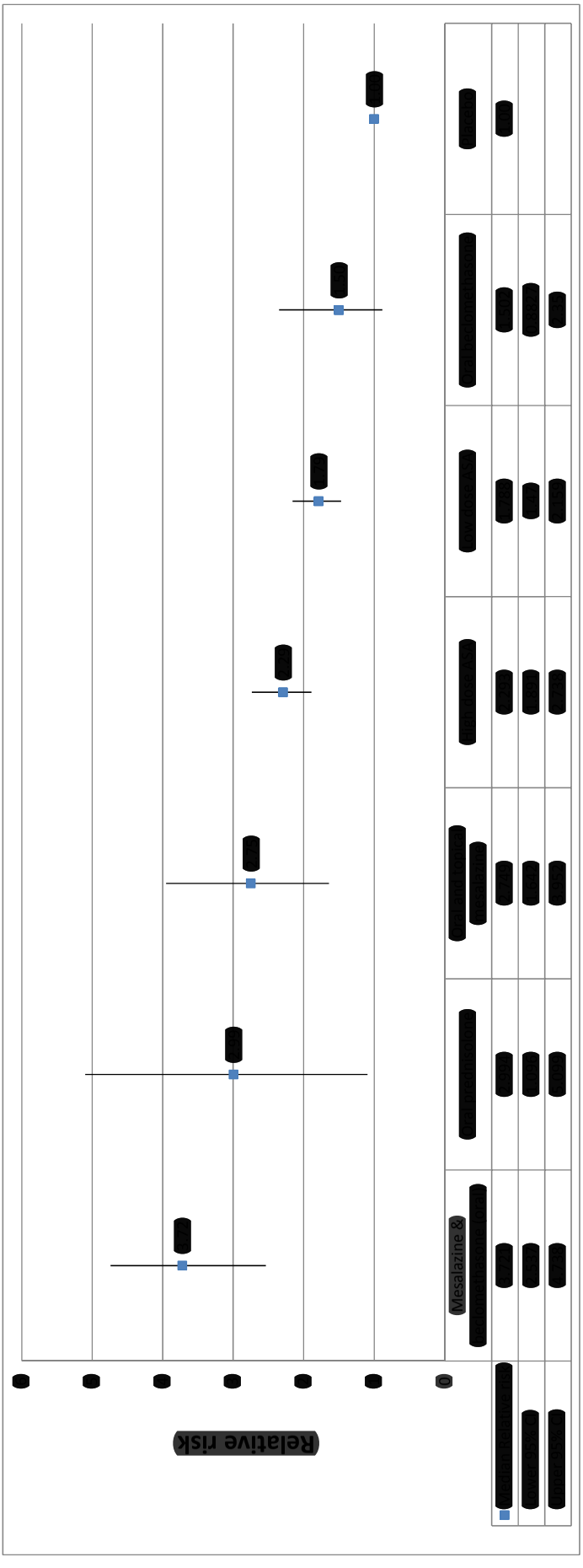

Median relative risk ratio compared to placebo for treatments based on the outcome of clinical remission – Fixed effects
Relative risk
Mesalazine &

Figure 294:

Table 13: The probability of each treatment being the best treatment for achieving clinical remission

Treatment	Probability of being the best treatment for achieving clinical remission – Fixed effects
Placebo	0%
Low dose ASA	0%
High dose ASA	0%
Oral prednisolone	28%
Oral beclometasone	0%
Mesalazine & beclometasone (oral)	64%
Oral and topical mesalazine	7%

Table 14: The log odds ratio compared to placebo for achieving clinical remission

Treatment	Mean	SD	2.5% CI	Median	97.5% CI
Low dose ASA	0.75	0.14	0.48	0.75	1.03
High dose ASA	1.13	0.15	0.83	1.13	1.44
Oral prednisolone	1.64	0.83	0.11	1.61	3.36
Oral beclometasone	0.51	0.34	-0.15	0.51	1.17
Mesalazine & beclometasone (oral)	2.11	0.42	1.30	2.10	2.95
Oral and topical mesalazine	1.45	0.42	0.63	1.44	2.27

2.4.2 Network 2: Withdrawals due to adverse events

19 studies from the baseline NMA were included in the withdrawals due to adverse events combined network, with four studies[37,49,56,117] being excluded due to one of its two comparators being high dose olsalazine.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots. A fixed effects model was run as per the baseline NMA.

Figure 295: Network for the proportion of people withdrawing from treatment due to adverse events (combined NMA)

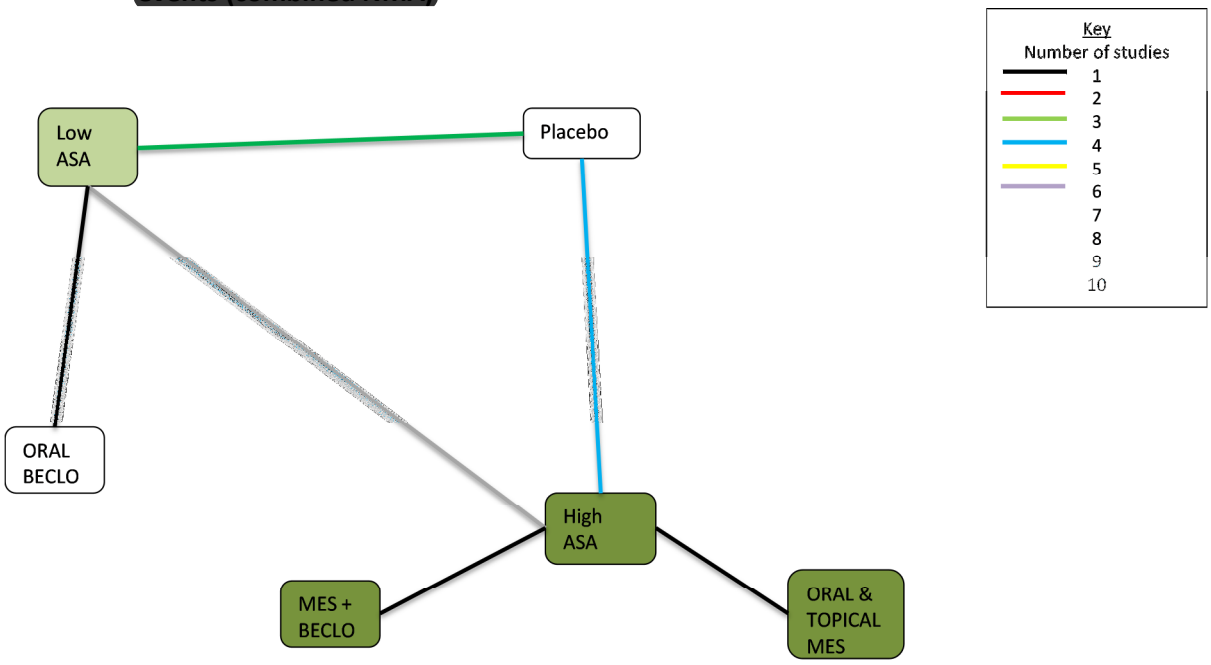


Table 15 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

Out of the treatments that were compared in the NMA, only high dose oral ASA had a statistically significant difference, which was demonstrated to have a lower withdrawals due to adverse events compared to placebo.

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (34.3) was close to the number of unconstrained data points (number of trial arms, n=41) indicating a reasonable goodness of fit for the model.

The probability of the treatment being the best (lower proportion of people withdrawing due to adverse events) was highest in oral mesalazine and beclometasone (80%).

Table 18 shows the log odds ratios which are the inputs used for the health economic model.

Table 15: Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people who withdrew due to adverse events at the end of the trial – Fixed effects

Placebo	0.77 (0.49, 1.21)	0.71 (0.41, 1.22)			
0.53 (0.80, 1.94)	Low dose ASA	0.75 (0.51, 1.11)	1.93 (0.18, 20.95)		
0.63 (0.40, 0.98)	0.78 (0.54, 1.13)	High dose ASA		0.35 (0.04, 3.27)	1.18 (0.45, 3.13)
1.78 (0.15, 10.68)	2.21 (0.20, 13.32)	2.83 (0.24, 17.38)	Oral beclometasone		
0.17 (0.01, 1.56)	0.21 (0.01, 1.90)	0.27 (0.01, 2.38)	0.09 (0.00, 2.58)	Mesalazine & beclometasone	
0.76 (0.24, 2.34)	0.95 (0.31, 2.86)	1.22 (0.42, 3.46)	0.43 (0.05, 6.26)	4.53 (0.40, 152.60)	Oral & topical mesalazine

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

NOTE: If no events occurred in one treatment arm, one was added to the numerator and denominator of all arms. This was also done for the direct comparisons, to ensure consistency.

Table 16: Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people who withdrew due to adverse events at the end of the trial – Fixed effects

Placebo	0.77 (0.49, 1.21)	0.71 (0.41, 1.22)			
0.53 (0.80, 1.94)	Low dose ASA	0.75 (0.51, 1.11)	1.93 (0.18, 20.95)		
0.63 (0.40, 0.98)	0.78 (0.54, 1.13)	High dose ASA		0.35 (0.04, 3.27)	1.18 (0.45, 3.13)
1.78 ((0.15, 10.68)	2.21 ((0.20, 13.32)	2.83 ((0.24, 17.38)	Oral beclometasone		
0.17 (0.01, 1.56)	0.21 (0.01, 1.90)	0.27 (0.01, 2.38)	0.09 (0.00, 2.58)	Mesalazine & beclometasone	
0.76 (0.24, 2.34)	0.95 (0.31, 2.86)	1.22 (0.42, 3.46)	0.43 (0.05, 6.26)	4.53 (0.40, 152.60)	Oral & topical mesalazine

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

NOTE: If no events occurred in one treatment arm, one was added to the numerator and denominator of all arms. This was also done for the direct comparisons, to ensure consistency.

Figure 296: Median relative risk ratio compared to placebo for treatments based on the outcome of withdrawals due to adverse events – Fixed effects

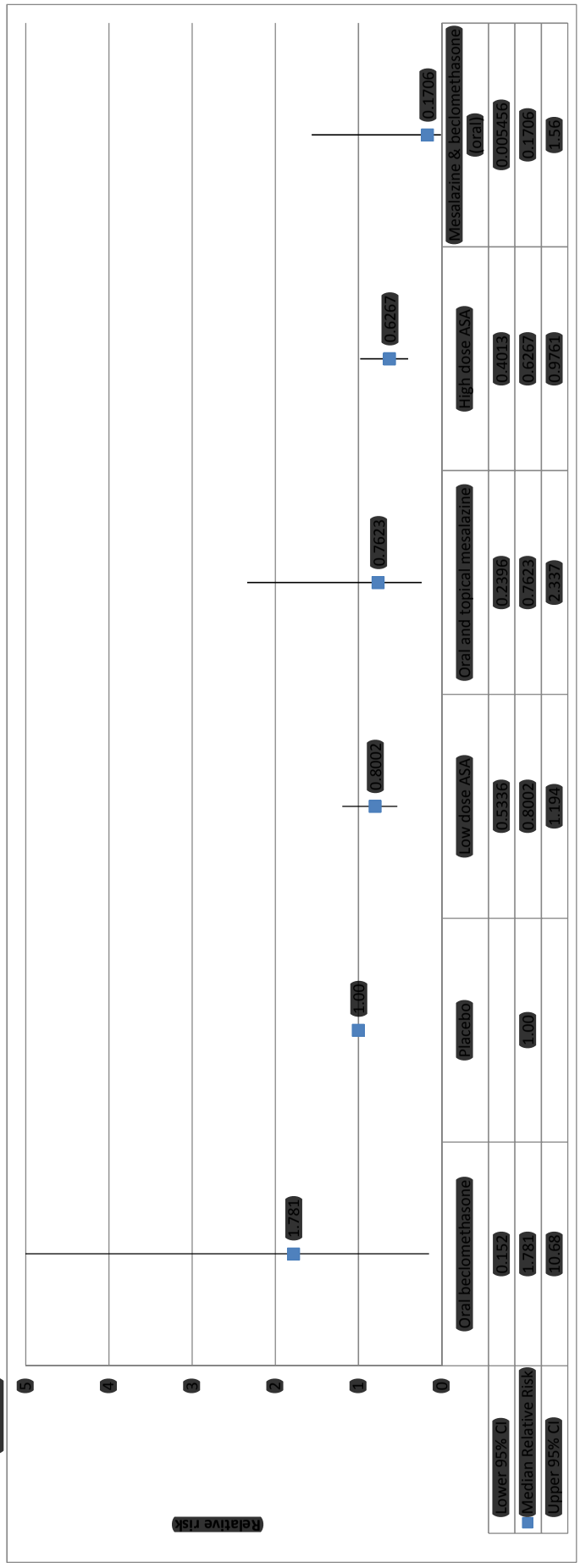


Table 17: Probability of being the best treatment for having the fewest withdrawals due to adverse events – Fixed effects

Treatment	Probability of being the best treatment for withdrawals due to adverse events – Fixed effects
Placebo	0%
Low dose ASA	1%
High dose ASA	6%
Oral beclometasone	6%
Mesalazine & beclometasone (oral)	80%
Oral and topical mesalazine	7%

Table 18: The log odds ratio compared to placebo for having the fewest withdrawals due to adverse events

Treatment	Mean	SD	2.5% CI	Median	97.5% CI
Low dose ASA	-0.24	0.22	-0.67	-0.24	0.19
High dose ASA	-0.50	0.24	-0.96	-0.50	-0.03
Oral beclometasone	0.77	1.54	-1.96	0.65	4.20
Mesalazine & beclometasone (oral)	-1.98	1.46	-5.29	-1.84	0.49
Oral and topical mesalazine	-0.28	0.63	-1.49	-0.29	0.97

2.5 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 5 and the Forest plots in Appendix H deciding upon the most effective intervention for the induction of remission of people with mild to moderate left sided or extensive ulcerative colitis is difficult. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons, NMA of the direct evidence were performed by preserving the trial randomization and minimizing bias.

Our analyses on people with left sided or extensive ulcerative colitis were based on a total of 28 studies of 10 different interventions (7 mono-therapies, 2 combination therapies). The studies formed a network for each outcome.

The findings from the NMA will be used to facilitate the GDG in decision making when developing recommendation for the induction of remission of people with left sided or extensive ulcerative colitis and as a base for the cost-effectiveness analysis.

Baseline NMA

In the first network of achieving clinical remission (author defined) by the end of the trial (≤12 weeks), the combination treatments (oral mesalazine & beclometasone, oral & topical mesalazine), balsalazide, prednisolone, high dose mesalazine and low dose mesalazine were significantly more effective than placebo. All of these treatments were also significantly better than low dose sulphasalazine. The combination treatment of mesalazine and beclometasone was significantly better than six other treatments and was found to have the highest probability of being the best treatment. The ranking of these treatments for median relative risks need to be interpreted with caution due to the large confidence intervals of the treatments effects and because they all overlap each other.

In the second network of achieving clinical improvement (author defined) by the end of the trial (≤12 weeks), the combination of mesalazine and beclometasone, oral and topical mesalazine, high dose mesalazine, high dose olsalazine, balsalazide and low dose mesalazine were significantly more effective than placebo. The combination treatment oral mesalazine and beclometasone was significantly better than all of the other treatments analysed apart from the other combination treatment (oral and topical mesalazine). Both the combination treatments were the most highly ranked with the greatest probability of being the most effective treatment.

In the third network of withdrawals due to adverse events by the end of the trial (≤12weeks), high dose olsalazine had a significantly higher event rate compared to the majority of other treatment options compared. Mesalazine and beclometasone combination treatment had the highest probability of the lowest withdrawals due to adverse events followed by balsalazide.

Combined NMA

Network 1 of the combined NMA also demonstrated the mesalazine and beclometasone dipropionate treatment combination to have a significantly higher proportion of people in clinical remission compared to low dose ASA, high dose ASA and oral beclometasone dipropionate alone. Again, it came out as having the highest probability of being the most effective treatment.

Network 2 of the combined NMA did not show any significant differences for withdrawals due to adverse events apart from high dose mesalazine which was lower than placebo. Similar to Network 1, the combination treatment of mesalazine and beclometasone dipropionate had the highest probability of being the best treatment, this time with the lowest withdrawals due to adverse events.

All of the networks seem to fit very well, as demonstrated by residual deviance and no inconsistencies in the networks found.

There was a lack of evidence for the 7 mono-therapies and 2 combination therapies included in the baseline NMA, for both the clinical remission and improvement outcomes at the different time points. The results would have been very limited (to two treatments), had to be taken in isolation and would not have had a meaningful result.

In summary, our NMA analysis on left sided or extensive ulcerative colitis networks focussed on three of the important clinical outcomes for assessing efficacy of medical treatments by 12 weeks.

Our NMA results should be considered within its following limitations:

- Firstly, the number of studies included for some comparisons, for example evaluating oral prednisolone there was only one trial which was relatively small and unblinded. That was the reason for observing the very wide confidence intervals in the relative risks for this drug
- The sample size of the studies comparing sulphasalazine were quite small (15-23 per arm), in addition to the limited number of studies assessing sulphasalazine (two studies)
- Many of the comparisons are based on single studies. The combination treatments which are favourably ranked are both based on single studies
- Due to the lack of published studies meeting our inclusion criteria, many treatments that could be used in the treatment of left sided or extensive colitis do not appear in our networks so it is unclear where those treatments would lie in the ranking of effectiveness for example, oral prednisolone for clinical improvement and withdrawals due to adverse events
- The studies varied in trial duration from 2-12 weeks which may have had an impact on the effectiveness of different treatments (less effective in shorter trials, more effective if a longer trial). We were unable to do a meaningful sensitivity analysis on this due to the lack of trial comparison data
- Many of the studies did not give a breakdown of the extent of the disease and are at risk of being an indirect population

- The studies used different indexes to assess clinical remission and improvement
- As with all meta-analyses, the studies available for analysis could be influenced by publication bias; however, no standardized methods have been fully developed to assess this type of bias in an NMA

It should be noted that this analysis did not take into account if the patients were on maintenance treatment when they had a relapse of ulcerative colitis. In the majority of studies where patients remained on maintenance treatment at a stable dose throughout the duration of the trial was not thought to have a significant impact on the results.

2.6 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the clinical reviews for the induction of remission of adults with mild to moderate left sided/ extensive ulcerative colitis even when direct comparative data was lacking.

Combination treatment, oral mesalazine and beclometasone came out as having the highest clinical remission and clinical improvement median relative risk ratios compared to placebo, and had the highest probability of being the most effective treatment with the fewest withdrawals due to adverse events. In the baseline NMA high dose olsalazine compared to the majority of treatments had significantly higher withdrawals due to adverse events.

2.7 Appendices

2.7.1 Excluded studies from the baseline NMA

Table 19: Studies from the direct clinical evidence review which were excluded from the baseline NMA

Study	Reason for exclusion
ANDUS2010[2]	Proctitis population
ARDIZZONE1999[3]	Preparation comparison
BARMEIR2003[5]	Proctitis and proctosigmoiditis population
BARON1962[7]	Prednisolone dosing only
BIANCONE2007[8]	Preparation comparison
BINDER1987/ANON1987[9]	Proctitis and proctosigmoiditis population
CAMPIERI1988[14]	Preparation comparison
CAMPIERI1990[13]	Proctosigmoiditis population
CAMPIERI1990A[15]	Proctitis and proctosigmoiditis population
CAMPIERI1991[16]	<50% left sided/ extensive disease
CAMPIERI1991A[17]	Unclear type of 5-ASA
CAMPIERI1993[18]	Mixed severity and dose comparison
CORTOT2008[21]	Preparation comparison
DANIELSSON1987[27]	Does not report any of the three outcomes
DHAENS2006[29]	MEZAVANT XL dose comparison
FARUP1995[34]	Proctitis and proctosigmoiditis population
FARUP2001[33]	Regimen comparison
FERRY1993[36]	Paediatric population
FORBES2005[38]	Mesalazine comparison

Study	Reason for exclusion
GIBSON2006[39]	Mesalazine comparison
GIONCHETTI1998[40]	Proctitis population
GROSS2006[44]	Proctitis and proctosigmoiditis population
GROSS2011[45]	<50% left sided/ extensive disease
HANAUER1998[48]	Proctitis and proctosigmoiditis population
HANAUER1998A[50]	Topical preparation comparison
HARTMAN2010[53]	<50% left sided/extensive disease. Note author defines left sided as >60cm.
JEWELL1974[61]	Immunomodulators are not included in the NMA
KOLKMAN2004[70]	Regimen comparison
KRUIS2003[71]	Dose was below low BNF dose, other doses were both high (so no comparator arm)
KRUIS2009[74]	Regimen comparison
LAMET2005[77] & 2011[76]	Regimen comparison
LAURITSEN1986[78]	Proctitis and proctosigmoiditis population
LEE1996[79]	<50% left sided/ extensive disease
LEMANN1995[80]	Topical preparation comparison
LINDGREN2002[84]	Dose comparison only
LOFTBERG1994[85]	Topical preparation comparison
MARAKHOUSKI2005[87]	Regimen comparison
MEYERS1987[89]	<50% left sided/ extensive disease
OGATA2006[99]	Immunomodulators are not included in the NMA
OREN1996[100]	Immunomodulators are not included in the NMA
POKROTNIEKS2000[102]	<50% left sided/ extensive disease
PORRO1994[104]	<50% left sided/ extensive disease
POWELLTUCK1978[105]	Regimen comparison
PRANTERA2005[107]	MEZAVANT XL comparison
RAEDLER2004[110]	Regimen comparison
RIJK1991[112]	Does not report any of the three outcomes
RIZZELLO2001[116]	Beclometasone dosing only
ROMANO2010[118]	Paediatric population
SOOD2002[127]	Preparation comparison
TARPILA1994[128]	Proctitis population
VANBODEGRAVEN1996[131]	Does not report any of the three outcomes
VECCHI2001[132]	<50% left sided/extensive disease
WILLIAMS1987[133]	Proctitis population
WILLOUGHBY1986[134]	Topical preparation comparison
ZINBERG1990[139]	<50% left sided/extensive disease

2.7.2 Additional excluded studies from the combined NMA

Table 20: Studies from the direct clinical evidence review which were excluded from the combined NMA

Study	Reason for exclusion

Study	Reason for exclusion
FEURLE1989[37]	High dose olsalazine treatment arm
HANAUER1996[49]	High dose olsalazine treatment arm
HETZEL1986[56]	High dose olsalazine treatment arm
JIANG2004[62]	High dose olsalazine treatment arm
ROBINSON1988[117]	High dose olsalazine treatment arm

2.7.3 WinBUGs codes

2.7.3.1 Random effects model

```
model{
for (i in 1:NS)
{
Events[i] <- r[i,1]*equals(t[i,1],1)
Numpatients[i] <- n[i,1]*equals(t[i,1],1)
}
totEvents<-sum(Events[])
totNumpatients<-sum(Numpatients[])
BR<- totEvents/totNumpatients
for(i in 1:NS){
w[i,1] < -0
delta [i,t[i,1]] < -0
mu[i] ~ dnorm(0,.0001)
for (k in 1:na[i])  {
r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]
rhat[i,k] <- p[i,t[i,k]] * n[i,k]
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
sdev[i]<- sum(dev[i,1:na[i]])
for (k in 2:na[i]) {
delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]
taud [i,t[i,k]] < -tau * 2 * (k - 1) / k
```

```
w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
sw[i,k] <-sum(w[i,1:k-1])/(k-1) }
}
d [1] <- 0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }
sd~dunif(0,2)
tau<-1/pow(sd,2)
rr [1] < -1
for (k in 2:NT)  {logit(v[k])<-logit(BR)+d[k]
rr[k]<-v[k]/BR
T[k]<-v[k]/BR}
sumdev <- sum(sdev[])
for (k in 1:NT) {
rk[k]<-NT+1-rank(rr[],k)
best[k]<-equals(NT+1-rank(rr[],k),1)}
for (c in 1:(NT-1))
{  for (k in (c+1):NT)
{  lor[c,k] <- d[k] - d[c]
log(or[c,k]) <- lor[c,k]
lrr[c,k] <- log(rr[k]) - log(rr[c])
log(rrisk[c,k]) <- lrr[c,k] } } }
```

2.7.3.2 Fixed effects model

```
model{
for (i in 1:NS)
{
Events[i] <- r[i,1]*equals(t[i,1],1)
Numpatients[i] <- n[i,1]*equals(t[i,1],1)
}
totEvents<-sum(Events[])
totNumpatients<-sum(Numpatients[])
BR<- totEvents/totNumpatients
```

```
(for(i in 1:NS){)
(#w[i,1] < -0)
(#delta [i,t[i,1]] < -0)
(mu[i] ~ dnorm(0,.0001)
(for (k in 1:na[i]) {
(r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
(logit(p[i,t[i,k]])<-mu[i] + d[t[i,k]] - d[t[i,1]]
(rhat[i,k] <- p[i,t[i,k]] * n[i,k]
(dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
(}
(sdev[i]<- sum(dev[i,1:na[i]])
(#for (k in 2:na[i]) {
(#delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
(#md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
(#taud [i,t[i,k]] < -tau * 2 * (k - 1) / k
(#w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])
(#sw[i,k] <-sum(w[i,1:k-1])/(k-1) }
(}
(d [1] <- 0
(for (k in 2:NT){d[k] ~ dnorm(0,.0001) }
(#sd~dunif(0,2)
(#tau<-1/pow(sd,2)
(rr [1] < -1
(for (k in 2:NT) {logit(v[k])<-logit(BR)+d[k]
(rr[k]<-v[k]/BR
(T[k]<-v[k]/BR}
(sumdev <- sum(sdev[])
(for (k in 1:NT) {
(rk[k]<-NT+1-rank(rr[],k)
(best[k]<-equals(NT+1-rank(rr[],k),1)}
(for (c in 1:(NT-1))
({ for (k in (c+1):NT)
```

{ lor[c,k] <- d[k] - d[c]

log(or[c,k]) <- lor[c,k]

lrr[c,k] <- log(rr[k]) - log(rr[c])

log(rrisk[c,k]) <- lrr[c,k] } } }

2.7.4 Treatment codes

2.7.4.1 Baseline NMA

2.7.4.1.1 Clinical remission

1. Placebo
2. Low dose mesalazine
3. High dose mesalazine
4. High dose olsalazine
5. Oral prednisolone
6. Balsalazide
7. Oral beclometasone
8. Mesalazine & beclometasone (oral)
9. Oral and topical mesalazine
10. Low dose SASP

2.7.4.1.2 Clinical improvement

1. Placebo
2. Low dose mesalazine
3. High dose mesalazine
4. Low dose SASP
5. High dose olsalazine
6. Balsalazide
7. Oral beclometasone
8. Mesalazine & beclometasone (oral)
9. Oral and topical mesalazine

2.7.4.1.3 Withdrawals due to adverse events

1. Placebo
2. Low dose mesalazine
3. High dose mesalazine

4. Low dose SASP
5. High dose olsalazine
6. Balsalazide
7. Oral beclometasone
8. Mesalazine & beclometasone (oral)
9. Oral and topical mesalazine

2.7.4.2 Combined NMA

2.7.4.2.1 Clinical remission

1. Placebo
2. Low dose ASA
3. High dose ASA
4. Oral prednisolone
5. Oral beclometasone
6. Mesalazine & beclometasone (oral)
7. Oral and topical mesalazine

2.7.4.2.2 Withdrawals due to adverse events

1. Placebo
2. Low dose ASA
3. High dose ASA
4. Oral beclometasone
5. Mesalazine & beclometasone (oral)
6. Oral and topical mesalazine

2.7.4.3 WinBUGS data code for the baseline NMA

2.7.4.3.1 Network 1 Clinical remission – fixed effects

```
list(
d=c(NA,0,0,0,0,0,0,0,0),
mu=c(-2,-3,0,1,0,0,-1,-1,1,-1,3,1,2,2,-3,1,3,-2,-3),
list(NS=19,NT=10)
r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]  t[,4]  t[,5]  na[]
 2 52 12 106 NA 1 NA 1 NA 1 1 2 NA NA NA 2
 19 86 64 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2
```

16 85 33 88 NA 1 NA 1 NA 1 1 2 NA NA NA 2

20 121 31 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

3 33 38 131 29 65 NA 1 NA 1 1 2 3 NA NA 3

11 90 28 97 28 95 NA 1 NA 1 1 2 3 NA NA 3

2 38 1 11 9 38 NA 1 NA 1 1 2 3 NA NA 3

12 90 27 183 NA 1 NA 1 NA 1 1 4 NA NA NA 2

3 18 9 19 NA 1 NA 1 NA 1 1 5 NA NA NA 2

19 83 64 166 NA 1 NA 1 NA 1 1 6 NA NA NA 2

121 383 152 389 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 63 13 60 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 24 11 24 NA 1 NA 1 NA 1 2 3 NA NA NA 2

28 49 44 50 NA 1 NA 1 NA 1 2 6 NA NA NA 2

38 89 38 84 NA 1 NA 1 NA 1 2 6 NA NA NA 2

50 87 46 90 NA 1 NA 1 NA 1 2 7 NA NA NA 2

21 61 34 58 NA 1 NA 1 NA 1 3 8 NA NA NA 2

16 56 25 71 NA 1 NA 1 NA 1 3 9 NA NA NA 2

15 21 10 21 NA 1 NA 1 NA 1 4 10 NA NA NA 2

END

2.7.4.4 Network 2 Clinical improvement – random effects

list(

d=c(NA,0,0,0,0,0,0,0,0),

sd=.2,

mu=c(1,-1,-1,-2,0,2,-3,2,2,1,2,-1,2,-2,0,-1,0,0,-3,-3,3,-1,-3),delta = structure(.Data = c(NA,-
3,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
3,NA,NA,NA,NA,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,0,3,NA,NA,NA,NA,NA,NA,NA,3,-
1,NA,NA,NA,NA,NA,NA,NA,NA,-2,-
1,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,1,NA,NA,NA,NA,NA,NA,NA,NA,0
(,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,2,NA,NA,NA,NA,NA,NA,NA,NA,1,NA,NA,NA,NA
(,NA,NA,NA,NA,-
1,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,NA,NA,NA,NA,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,2,NA,NA
(,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-
3,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,2,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,3,NA,NA,NA,NA,NA,NA,NA,NA,)
(NA,0,NA,NA,NA,NA,3,NA,NA,NA,NA)

),.Dim=c(23 , 9))))

(list(NS=23,NT=9))

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[])

8 52 28 106 NA 1 NA 1 NA 1 1 2 NA NA NA 2

34 86 99 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2

22 85 49 88 NA 1 NA 1 NA 1 1 2 NA NA NA 2

30 121 42 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

49 90 77 97 80 95 NA 1 NA 1 1 2 3 NA NA 3

9 33 61 131 41 65 NA 1 NA 1 1 2 3 NA NA 3

7 38 3 11 28 38 NA 1 NA 1 1 2 3 NA NA 3

9 23 14 21 NA 1 NA 1 NA 1 1 4 NA NA NA 2

2 15 6 15 NA 1 NA 1 NA 1 1 5 NA NA NA 2

16 48 25 50 NA 1 NA 1 NA 1 1 5 NA NA NA 2

8 20 13 20 NA 1 NA 1 NA 1 1 5 NA NA NA 2

33 83 92 166 NA 1 NA 1 NA 1 1 6 NA NA NA 2

21 52 19 58 NA 1 NA 1 NA 1 2 3 NA NA NA 2

77 139 89 129 NA 1 NA 1 NA 1 2 3 NA NA NA 2

77 150 76 136 NA 1 NA 1 NA 1 2 3 NA NA NA 2

251 383 273 389 NA 1 NA 1 NA 1 2 3 NA NA NA 2

27 63 45 60 NA 1 NA 1 NA 1 2 3 NA NA NA 2

11 24 18 24 NA 1 NA 1 NA 1 2 3 NA NA NA 2

22 51 22 53 NA 1 NA 1 NA 1 2 6 NA NA NA 2

59 87 57 90 NA 1 NA 1 NA 1 2 7 NA NA NA 2

31 61 44 58 NA 1 NA 1 NA 1 3 8 NA NA NA 2

29 56 51 71 NA 1 NA 1 NA 1 3 9 NA NA NA 2

15 21 20 21 NA 1 NA 1 NA 1 4 5 NA NA NA 2

END

2.7.4.5 Network 3 Withdrawals due to adverse events – fixed effects

list(

d=c(NA,0,0,0,0,0,0,0),

mu=c(3,0,-3,-2,-3,-3,2,3,-2,-2,-1,0,-3,-3,2,-1,-3,2,1,2,2,2,-3),

list(NS=23,NT=9)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[])

2 86 2 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2

1 53 3 107 NA 1 NA 1 NA 1 1 2 NA NA NA 2

11 85 5 88 NA 1 NA 1 NA 1 1 2 NA NA NA 2

10 121 7 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

11 90 9 97 7 95 NA 1 NA 1 1 2 3 NA NA 3

1 34 6 132 3 66 NA 1 NA 1 1 2 3 NA NA 3

2 38 1 11 1 38 NA 1 NA 1 1 2 3 NA NA 3

1 24 3 22 NA 1 NA 1 NA 1 1 4 NA NA NA 2

1 54 4 53 NA 1 NA 1 NA 1 1 5 NA NA NA 2

1 16 3 16 NA 1 NA 1 NA 1 1 5 NA NA NA 2

1 48 3 50 NA 1 NA 1 NA 1 1 5 NA NA NA 2

2 90 17 183 NA 1 NA 1 NA 1 1 5 NA NA NA 2

10 83 15 166 NA 1 NA 1 NA 1 1 6 NA NA NA 2

4 139 4 129 NA 1 NA 1 NA 1 2 3 NA NA NA 2

8 150 5 136 NA 1 NA 1 NA 1 2 3 NA NA NA 2

15 383 15 389 NA 1 NA 1 NA 1 2 3 NA NA NA 2

3 64 1 61 NA 1 NA 1 NA 1 2 3 NA NA NA 2

1 49 1 50 NA 1 NA 1 NA 1 2 6 NA NA NA 2

6 89 3 84 NA 1 NA 1 NA 1 2 6 NA NA NA 2

5 51 1 53 NA 1 NA 1 NA 1 2 6 NA NA NA 2

1 88 2 91 NA 1 NA 1 NA 1 2 7 NA NA NA 2

3 61 1 58 NA 1 NA 1 NA 1 3 8 NA NA NA 2

6 56 9 71 NA 1 NA 1 NA 1 3 9 NA NA NA 2

END

2.7.4.6 WinBUGS data code for the combined NMA

2.7.4.6.1 Network 1 Clinical remission – fixed effects

list(

d=c(NA,0,0,0,0,0,0),

mu=c(-3,-1,2,3,3,0,-3,-3,-3,-1,0,0,-2,-2,-3,0,-1),

list(NS=17,NT=7)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[])

2 51 12 103 NA 1 NA 1 NA 1 1 2 NA NA NA 2

19 84 64 170 NA 1 NA 1 NA 1 1 2 NA NA NA 2

16 74 33 83 NA 1 NA 1 NA 1 1 2 NA NA NA 2

20 121 31 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

3 32 38 125 29 62 NA 1 NA 1 1 2 3 NA NA 3

11 79 28 88 28 88 NA 1 NA 1 1 2 3 NA NA 3

2 36 1 10 9 37 NA 1 NA 1 1 2 3 NA NA 3

19 73 64 151 NA 1 NA 1 NA 1 1 3 NA NA NA 2

3 18 9 19 NA 1 NA 1 NA 1 1 4 NA NA NA 2

121 368 152 374 NA 1 NA 1 NA 1 2 3 NA NA NA 2

28 48 44 49 NA 1 NA 1 NA 1 2 3 NA NA NA 2

38 83 38 81 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 63 13 60 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 24 11 24 NA 1 NA 1 NA 1 2 3 NA NA NA 2

50 86 46 88 NA 1 NA 1 NA 1 2 5 NA NA NA 2

21 58 34 57 NA 1 NA 1 NA 1 3 6 NA NA NA 2

16 56 25 71 NA 1 NA 1 NA 1 3 7 NA NA NA 2

END

2.7.4.7 Network 2 Withdrawals due to adverse events – fixed effects

list(

d=c(NA,0,0,0,0,0),

mu=c(3,-3,1,1,1,2,1,0,-3,0,2,1,0,2,2,-3,2,0,0),

list(NS=19,NT=6)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[])

2 86 2 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2

1 53 3 107 NA 1 NA 1 NA 1 1 2 NA NA NA 2

11 85 5 88 NA 1 NA 1 NA 1 1 2 NA NA NA 2

1 24 3 22 NA 1 NA 1 NA 1 1 2 NA NA NA 2

10 121 7 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

11 90 9 97 7 95 NA 1 NA 1 1 2 3 NA NA 3

1 34 6 132 3 66 NA 1 NA 1 1 2 3 NA NA 3

2 38 1 11 1 38 NA 1 NA 1 1 2 3 NA NA 3

10 83 15 166 NA 1 NA 1 NA 1 1 3 NA NA NA 2

4 139 4 129 NA 1 NA 1 NA 1 2 3 NA NA NA 2

8 150 5 136 NA 1 NA 1 NA 1 2 3 NA NA NA 2

15 383 15 389 NA 1 NA 1 NA 1 2 3 NA NA NA 2

1 49 1 50 NA 1 NA 1 NA 1 2 3 NA NA NA 2

6 89 3 84 NA 1 NA 1 NA 1 2 3 NA NA NA 2

5 51 1 53 NA 1 NA 1 NA 1 2 3 NA NA NA 2

3 64 1 61 NA 1 NA 1 NA 1 2 3 NA NA NA 2

1 88 2 91 NA 1 NA 1 NA 1 2 4 NA NA NA 2

3 61 1 58 NA 1 NA 1 NA 1 3 5 NA NA NA 2

6 56 9 71 NA 1 NA 1 NA 1 3 6 NA NA NA 2

END

(Note: r[], number of events by trial arm; n[], total number of participants by trial arm; t[], treatment code; na[], number of trial arms)

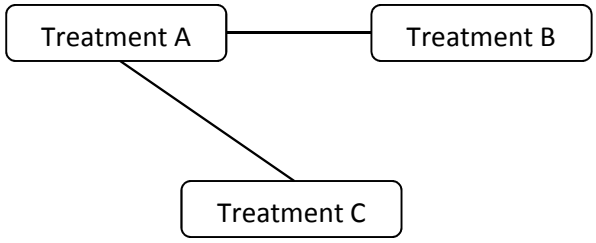
3 Appendix J: Maintenance NMA

Network meta-analysis of medical treatments for the maintenance of remission in people with left sided or extensive ulcerative colitis

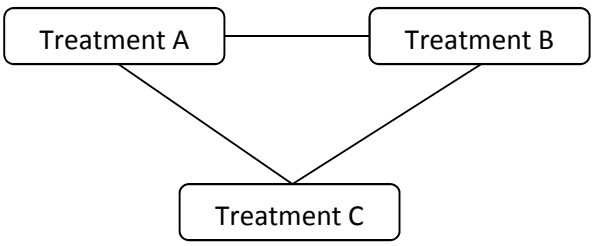
3.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in Chapter 7 and the Forest plots in Appendix H) does not help inform which intervention is the most effective for the maintenance of remission in people with left-sided or extensive ulcerative colitis. The challenge of interpretation has arisen for three reasons:

- In isolation, each pair-wise comparison (for example; oral mesalazine versus oral balsalazide) does not inform the choice among treatments.
- Direct evidence is not available for some pair-wise comparisons in randomised controlled trials (for example; oral balsalazide versus oral sulphasalazine). In the example below there are no trials looking at treatment B versus treatment C.



- There are frequently multiple overlapping comparisons known as “closed loops” in the NMA where the estimates of an effect have been calculated either within the same trial or from multiple trials. Different trials may give slightly different point estimates



To overcome these issues, a hierarchical Bayesian Network Meta-analysis (NMA) was performed. This type of analysis allows the synthesis of data from direct and indirect comparisons without breaking randomisation and the ranking of different interventions. In this case, in order of efficacy, the following networks have been reviewed:

- Rate of relapse (author definition) by the end of the trial (minimum 6 months)
- Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

The analysis provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Two NMAs run, the first being the baseline scenario and the second which combined aminosalicylates into low and high doses.

For the baseline NMA, in order of efficacy, the following networks have been reviewed:

- Rate of relapse (author definition) by the end of the trial (minimum 6 months)
- Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

For the combined NMA, the following networks have been reviewed:

- Rate of relapse (author definition) by the end of the trial (minimum 6 months)
- Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

The analysis provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

3.2 Methods

3.2.1 Study selection and data collection

To estimate treatment effects of the different drugs used for the maintenance of remission, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular maintenance of remission strategy was derived only from randomised controlled trials that had that particular treatment in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on selected studies that matched the pre-defined NMA protocol. Doses of the drugs in the included RCTs were classed as low and high as defined by the GDG.

Therefore, two networks of evidence were identified, defined by population and outcome measure.

For adults, young people and children with in remission who had previously had a mild to moderate flare of left sided or extensive ulcerative colitis:

- Network 1: Rate of relapse (author definition) by the end of the trial (minimum 6 months)

- Network 2: Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

To review the NMA protocol, see Appendix C.

3.2.2 Outcome measures

The NMA evidence reviews considered one clinical efficacy outcome - the rate of relapses. This was one of the clinical efficacy outcomes identified from the clinical evidence review and considered by the GDG as the most important clinical outcome. The second outcome was any form of withdrawals from treatment. This was used rather than withdrawals due to treatment specific adverse events due to unclear reporting in the trials.

3.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical review already presented in Chapter 7 of the full guideline and the Forest plots in Appendix H of the full guideline. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the network meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded (see page 187 for excluded studies from the baseline NMA and combined NMA).

The treatments included in each network for each NMA are shown in Table 21.

Table 21: Maintenance of remission treatments included in the network meta-analyses of people in remission with ulcerative colitis

Baseline Network Meta-Analysis		Combined Network Meta-Analysis	
Network 1: Relapse	**Network 2: Withdrawals**	**Network 1: Relapse**	**Network 2: Withdrawals**
Placebo	Placebo	Placebo	Placebo
High dose Pentasa	High dose Pentasa	Low dose ASA	Low dose ASA
Low dose Asacol	Low dose Asacol	High dose ASA	High dose ASA
High dose Asacol	High dose Asacol		
Low dose Olsalazine	Low dose Olsalazine		
High dose Olsalazine	High dose Olsalazine		
Low dose SASP	Low dose SASP		
High dose SASP	High dose SASP		
Low dose Salofalk	Low dose Salofalk		
High dose Salofalk	High dose Salofalk		
Low dose Balsalazide	Low dose Balsalazide		
High dose Balsalazide	High dose Balsalazide		

3.2.4 Statistical analysis

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome a diagram of the evidence network was produced (see Figure 278 and Figure 299).

Network 1: Relapse

Some trials eligible for inclusion in the NMA reported relapses in terms of hazard ratio. The remainder of the trials reported cumulative count statistics; that is the number of people who had a relapse at a specific time point. In order to combine data from all the studies, a multi-statistic evidence synthesis using WinBUGS version 1.4 software was conducted according to methodology

described by Woods 2010[135].This allowed hazard ratio statistics and cumulative count statistics to be combined within a single network meta-analysis on the log hazard scale. The count statistics used are presented in Table 3. The relapse data was made conditional on not having withdrawn from treatment. In order to do this, for studies that reported count statistics, the number of people who withdrew from the study was excluded from the number of people who completed the study. The proportion of people who relapsed was then based on the number of people left in the study.

The hazard ratio statistics are presented in Table 24, along with the derived estimates of the mean log hazard ratio and its standard error. These were calculated using the formulae below:

$$\overline{\boldsymbol{In(HR)}} = \frac{\boldsymbol{In(HRuci)} + \boldsymbol{In(HRlci)}}{\mathbf{2}}$$

$$\boldsymbol{se} = \frac{\boldsymbol{In(HRuci)} - \boldsymbol{In(HRlci)}}{\mathbf{2} \times \mathbf{1.96}}$$

A random effects analysis of the network was conducted. Random effects models allow for the possibility that the true treatment effect may differ between trials. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 10,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The output from the NMA was treatment-specific log hazards. The overall ranking of treatments compared to placebo was calculated. In addition, the proportion of simulations of the Markov chain in which each intervention had the lowest log hazard was recorded.

Network two: Withdrawals

A hierarchical Bayesian network meta-analysis was performed using WinBUGS version 1.4 software. A three-arm random effects logistic regression model template, obtained from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html) was adapted. This model accounts for the correlation between study level effects induced by multi-arm trials. The parameters were estimated by Markov chain Monte Carlo simulation. Random effects models allow for the possibility that the true treatment effect may differ between trials. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000. Any study that reported no events in any of the arms was excluded.

For the analyses, a series of 10,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for the response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\widetilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\widetilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\widetilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks($\boldsymbol{rr_b}$):

$$\boldsymbol{p_b} = \frac{\boldsymbol{e}^{\boldsymbol{BO}}}{\mathbf{1} + \boldsymbol{e}^{\boldsymbol{BO}}}$$

$$\boldsymbol{rr_b} = \frac{\boldsymbol{p}}{\boldsymbol{p_b}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensure that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

Differences between treatments were considered significant at the 0.05 level if the 95% credible interval for the RR did not cross 1.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Tests for inconsistency

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations (e.g. populations of mixed disease extent, age)
- Use of concomitant medications
- Different doses for drug treatments other than oral ASAs were the doses were not taken into account
- Different trial durations (longer trials are likely to have a higher proportion of patients achieving the outcome)
- Quality of the study (risk of bias)
- Different indexes and thresholds used to determine clinical remission and improvement

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the hazard ratios from the direct evidence (from pair-wise meta-analysis) to the hazard ratios from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the hazard ratio from the NMA did not fit within the confidence interval of the hazard ratio from the direct comparison.

3.3 Baseline NMA results

A total of 18 studies met the inclusion criteria and were included in either or both of the networks. Table 22 below gives a summary of the characteristics of included studies.

Table 22: Baseline characteristics of included studies in the network meta-analysis

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
MINER1995 48 week trial	4g mesalazine (Pentasa) versus placebo	18 years or older Previously diagnosed ulcerative colitis in remission (sigmoidoscopic index of <5, mean of <5 stools/day, absence of rectal bleeding)	Pan colitis or left sided colitis.	Prior use of various medications, oral steroid, rectal therapy and sulphasalazine. Immunosuppressants and oral/rectal steroids required a 90 and 60 day wash out respectively, prior to baseline	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given >10% difference in missing data between the treatment arms
HANAUER1996A 6 month trial	1.6g mesalazine (Asacol) versus placebo The 0.8g mesalazine arm has not been included as it is below the recommended dosing regimen.	18-75 years In remission for at least 1 month as indicated by the endoscopic appearance of the bowel and by the passage of five or fewer bloodless stools per day	All extents of disease. >50% left sided or extensive in the two treatment groups.	Previously treated with 2-4g sulphasalazine per day or 0.8-1.6g of any oral mesalazine per day. Dose had to be kept constant for at least 1 month before study entry.	Relapse	Unclear allocation concealment Unclear who dropped out from which treatment group Double blind but no further information was given
WRIGHT1993 12 month trial	2g olsalazine versus placebo	18-75 years Inactive UC diagnosed by Truelove & Witts criteria	No restrictions described. Unable to calculate % with left sided/ extensive colitis.	Unknown. Therapy of last attack was described (oral and/or rectal corticosteroids).	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
ARDIZZONE1999c 12 month trial	1.2g mesalazine (Asacol) versus placebo	18-75 years Confirmed diagnosis of intermittent chronic ulcerative colitis in stable remission for at least 1 month	All extents of disease. >50% left sided or extensive colitis in the two treatment groups.	2g/ day of sulphasalazine or 0.8-1.5g mesalazine/ day	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given
COURTNEY1992 12 month trial	1g olsalazine versus 1.5g mesalazine (Asacol)	16-75 years UC in remission	All extents >50% left sided or extensive colitis	Unknown.	Relapse Withdrawals	Single blind
GREEN1998A 12 month trial	3g balsalazide versus 1.2g mesalazine (Asacol)	18-80 years UC symptoms requiring treatment with maintenance therapy. Remission declared up to a maximum of 1 year before entry to the study	Not described.	Some patients had previous use of balsalazide or mesalazine in the last year.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment no extent data given at baseline High dropout rate (but <10% difference between treatment arms)
IRELAND1988 6 month trial	1g olsalazine versus 2g sulphasalazine	17-75 years UC in remission, no relapse for 6 months	All extents >50% left sided or extensive colitis	Majority of the patients were on sulphasalazine prior to the trial	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Stated to be double blind but no further information was given

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
NILSSON1995 6 month trial	1g olsalazine versus 2g sulphasalazine	Age inclusion not described. Remission for the last 2 months, with at least 2 episode of active colitis during the last 5 years	All extents. >50% left sided or extensive colitis	Sulphasalazine tolerant population.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Stated to be double blind but no further information was given
DISSANAYAKE1973 6 month trial	2g sulphasalazine versus placebo	Age inclusion not described. Prolonged remission while on sulphasalazine maintenance therapy.	Not described.	Sulphasalazine 0.5g, 4 times a day.	Relapse There were no withdrawals	Unclear method of randomisation No baseline characteristics data given
SANDBERGGERTZEN1986 6 month trial	1g olsalazine versus placebo	No age limits Patients who after 6 months of medication with olsalazine were in remission and off steroids. If patients were not in remission at the start of the trial they were re-evaluated at 2 months and if in remission, they were then entered into the trial.	No extent limit. Unclear what percentage was left sided/extensive (**note:** subgroup data on extensive disease has been used in the analysis).	Patients were unable to tolerate sulphasalazine. They had all previously been on olsalazine.	Relapse There were no withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given Very limited baseline characteristics
PAOLUZI2005 12 month trial	1.2g mesalazine (Asacol) versus 2.4g mesalazine (Asacol)	>18 years Recent disease relapse (within the last 3 months) prior to the study who have been appropriately treated until remission had been achieved.	>20cm from the anus. >50% left sided or extensive colitis.	Previous activity was mild to moderate disease and the treatment consisted of oral and topical mesalazine.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Single blind, open label

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
TRAVIS1994 12 month trial	1g olsalazine versus 2g olsalazine	Age inclusion not described. Remission for 3 months or more	No restriction described. >50% left sided or extensive colitis.	Unknown.	Relapse	Unclear method of randomisation and allocation concealment Unclear blinding Unclear dropout rate Unclear outcome assessment
KRUIS1995 6 month trial	1.25g olsalazine versus 2g olsalazine versus 2g sulphasalazine	15-77 years Remission for less than 12 months	All extents Two treatment groups have 50% left sided or extensive colitis.	Unknown.	Relapse Withdrawals are not reported by subgroup, only overall	Unclear allocation concealment States to be double blind, there was no information given on physician blinding >10% difference in missing data between some of the treatment arms
RIJK1992 48 week trial	2g olsalazine versus 4g sulphasalazine	16-78 years Remission for not longer than 2 years. Active UC in the past.	Unclear the % of left sided and extensive colitis	Unknown.	Relapse Withdrawals	Unclear method randomisation and allocation concealment Limited baseline characteristics >10% difference in missing data between the treatment arms Double blind but

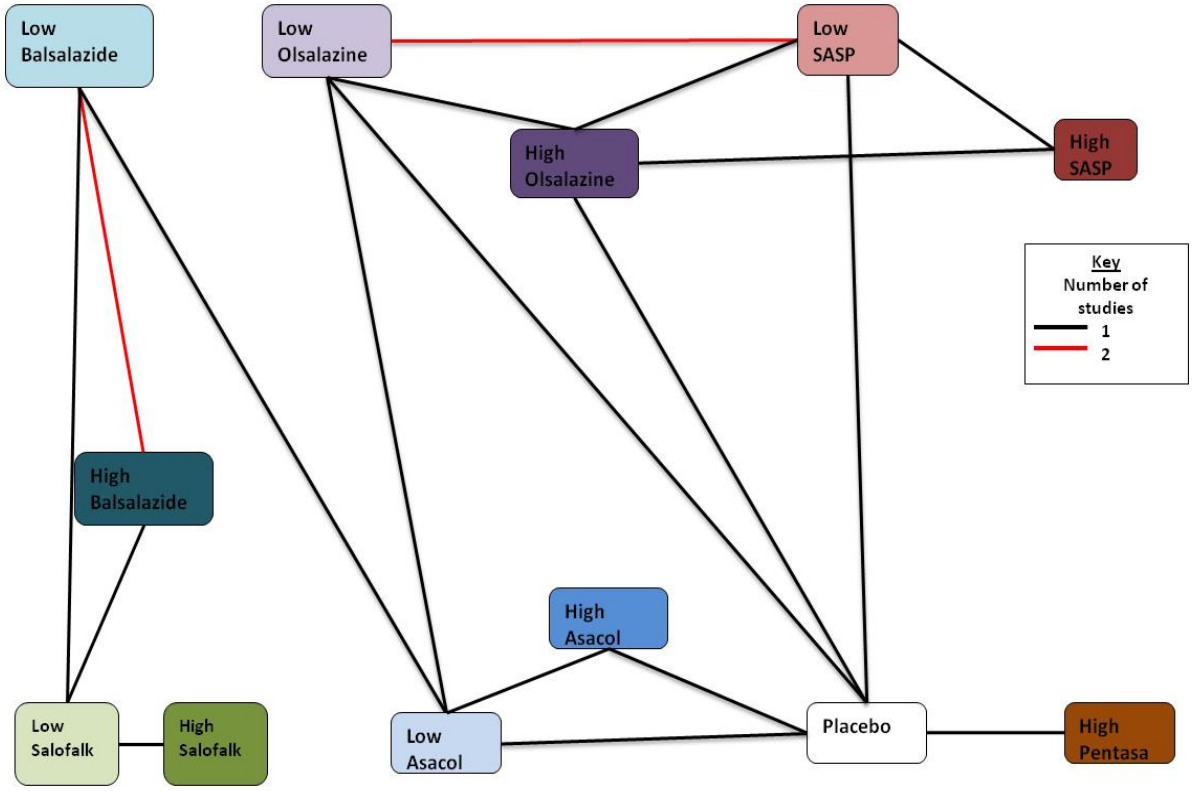
Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
						no further information was given
AZADKHAN1980 6 month trial	2g sulphasalazine versus 4g sulphasalazine	Age inclusion not described. Just states ulcerative colitis needs to be in remission as the inclusion criteria.	No restriction described. Unknown extent.	163/170 patients were on 2g sulphasalazine prior to the trial.	Relapse No withdrawals	Unclear method of randomisation and allocation concealment Unclear blinding Very limited baseline characteristics
GREEN1992 12 month trial	3g balsalazide versus 6g balsalazide	19-78 years Clinical and sigmoidoscopic remission	≥15cm at some point in their illness. >50% left sided or extensive colitis.	All were maintained on a 5-ASA preparation alone prior to the trial.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given
KRUIS2001 26 week trial	3g balsalazide versus 6g balsalazide versus 1.5g mesalazine (Salofalk)	18-70 years Clinical and endoscopic remission with a history of at least 2 previous attacks	UC involving at least the rectum and sigmoid colon >50% left sided or extensive colitis	Around 50% had used 5-ASA prior to the trial.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given >10% difference in missing data between two treatment arms
KRUIS2011	1.5g mesalazine	18-75 years	Mucosal	Unclear what previous	Relapse	

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
12 month trial	(Salofalk) versus 3.0g mesalazine (Salofalk)	Last active episode had ended within the 3 months prior to study entry	inflammation extending at least 15cm. No further details are given.	treatment was. Information only given for treatment of last acute episode.	Withdrawals	

3.3.1 Network 1: Relapse

A total of 18 studies[4,22,32,41,42,47,58,72,73,75,91,98,101,113,119,129,136] from the original evidence review met the inclusion criteria and reported relapse as an outcome. Figure 278 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason (s) for exclusion on page 187.

Figure 297: Network for the proportion of people having a relapse (baseline NMA)



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

There were 11 double blind trials, two single blind and five with unclear blinding. 17 trials had an unclear method of randomisation, allocation concealment or both. In seven studies, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. There were nine studies that included adults ≥18 years, five studies that included some young people with their inclusion criteria being 16-78 years and 15-77 years, 17-75 years, 16-75 years and five studies did not describe the age inclusion criteria.

The data from the 18 studies included in the NMA are presented below. Table 3 lists studies that provided relapse data in the form of count statistics. Table 24 lists studies that provided relapse data in form of hazard ratios.

Table 23: Relapse data: studies reporting count statistics

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
Dissanayake 1973	Placebo	SASP (2g)	NA	17	31	4	33	NA	NA
Sandberg-Gertzen 1986	Placebo	Olsalazine (1g)	NA	22	49	12	52	NA	NA
Paolezi 2005	Asacol (1.2g)	Asacol (2.4g)	NA	48	68	48	72	NA	NA
Travis 1994	Olsalazine (2g)	Olsalazine (1g)	NA	10	62	17	65	NA	NA
Kruis 1995	Olsalazine (2g)	SASP (2g)	NA	5	29	11	36	NA	NA
Rijk 1982	Olsalazine (2g)	SASP (4g)	NA	6	15	7	19	NA	NA
Azadkhan 1980	SASP (2g)	SASP (4g)	NA	8	57	5	56	NA	NA
Green 1992	Balsalazide (3g)	Balsalazide (6g)	NA	10	44	15	47	NA	NA
Kruis 2001	Balsalazide (3g)	Balsalazide (6g)	Salofalk (1.5g)	13	27	3	34	6	29
Kruis 2011	Salofalk (1.5g)	Salofalk (3g)	NA	44	195	17	193	NA	NA

Table 24: Relapse data: studies reporting hazard ratio

Study	Treatment	Base	HR	HR (LCI)	HR (UCI)	LN(HR)	se (LN(HR))
Miner 1995	Pentasa (4g)	Placebo	0.63	0.41	0.96	-0.46	0.22
Hanauer 1996A	Asacol (1.6g)	Placebo	0.47	0.27	0.84	-0.76	0.29
Wright 1993	Olsalazine (2g)	Placebo	0.52	0.29	0.92	-0.65	0.29
Adrizzone 1999c	Asacol (1.2g)	Placebo	0.60	0.18	1.97	-0.51	0.61
Courtney 1992	Olsalazine (1g)	Asacol (1.2g)	0.30	0.11	0.84	-1.20	0.52
Green 1998A	Balsalazide (3g)	Asacol (1.2g)	0.74	0.36	1.55	-0.30	0.37
Ireland 1988	Olsalazine (1g)	SASP (2g)	1.84	0.83	4.05	0.61	0.40

Study	Treatment	Base	HR	HR (LCI)	HR (UCI)	LN(HR)	se (LN(HR))
Nilsson 1995	Olsalazine (1g)	SASP (2g)	1.28	0.89	1.85	0.25	0.19

Table 25 summaries the results of the conventional meta-analyses and the NMA in terms of hazard ratios (HRs). The white area contains data generated from studies directly comparing different interventions (head to head comparisons) while the results of the NMA are presented in the grey area.

Out of the treatments that were compared in the NMA, low and high doses of olsalazine and low and high doses of sulfasalazine were found to be significantly better than placebo (Table 25).

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

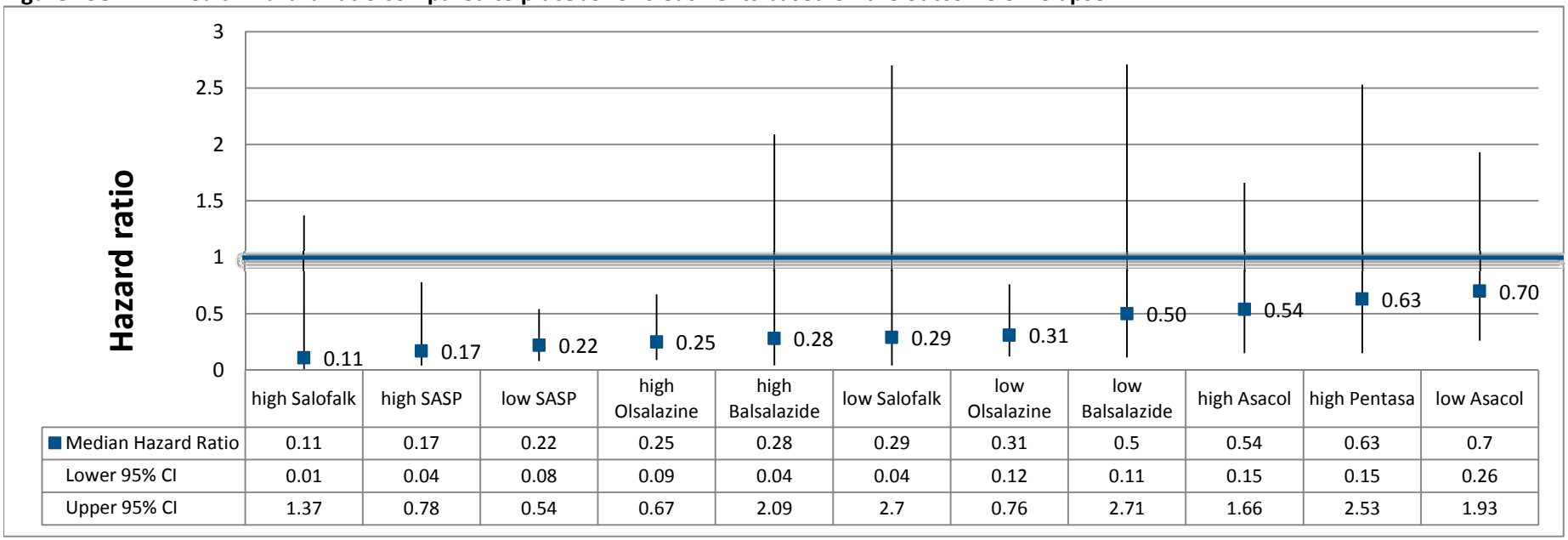
The median hazard ratio of all treatments compared to placebo is shown in Figure 298. Again it shows that low and high doses of olsalazine and low and high doses of sulfasalazine are significantly better than placebo. However, due to the overlapping confidence intervals of the different treatments, it is felt that there is insufficient evidence to be confident of one treatment's superiority compared to the alternative treatment for the maintenance of remission compared to placebo.

Table 25: Hazard ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the rate of relapse

Placebo	**0.63 (0.41,0.96)**	**0.47 (0.27,0.84)**	**0.41 (0.23,0.73)**	0.60 (0.18,1.97)							
0.63 (0.15,2.53)	**high Pentasa**										
0.54 (0.15,1.66)	0.88 (0.15,5.5)	**high Asacol**									
0.25 (0.09,0.67)	0.4 (0.07,2)	0.46 (0.08,1.76)	**high Olsalazine**								
0.70 (0.26,1.93)	1.08 (0.18,6.69)	1.24 (0.34,3.81)	2.71 (0.81,12.11)	**low Asacol**		**0.30 (0.11,0.84)**	0.74 (0.36,1.55)				
0.22 (0.08,0.54)	0.35 (0.06,1.95)	0.4 (0.08,1.67)	0.88 (0.33,2.71)	0.33 (0.08,1.14)	**low SASP**	1.36 (0.98,1.90)					
0.31 (0.12,0.76)	0.5 (0.09,2.61)	0.57 (0.13,2.13)	1.25 (0.5,3.74)	0.46 (0.14,1.39)	1.43 (0.62,3.4)	**low Olsalazine**					
0.5 (0.11,2.71)	0.79 (0.06,9.31)	0.92 (0.1,5.93)	2.00 (0.26,20.32)	0.74 (0.15,3.39)	2.32 (0.27,20.73)	1.62 (0.2,13.08)	**low Balsalazide**				
0.17 (0.04,0.78)	0.28 (0.04,1.89)	0.31 (0.05,1.77)	0.69 (0.2,2.7)	0.25 (0.05,1.29)	0.79 (0.21,2.93)	0.56 (0.13,2.24)	0.35 (0.03,3.78)	**high SASP**			
0.29 (0.04,2.7)	0.45 (0.02,7.61)	0.52 (0.03,5.72)	1.14 (0.08,18.37)	0.42 (0.04,3.76)	1.30 (0.09,17.95)	0.92 (0.07,11.19)	0.57 (0.11,2.48)	1.65 (0.1,33.26)	**low Salofalk**		
0.11 (0.01,1.37)	0.16 (0.01,3.7)	0.18 (0.01,2.86)	0.4 (0.02,8.54)	0.15 (0.01,1.8)	0.46 (0.02,8.39)	0.32 (0.02,5.79)	0.2 (0.03,1.45)	0.58 (0.02,13.96)	0.35 (0.08,1.31)	**high Salofalk**	
0.28 (0.04,2.09)	0.45 (0.03,6.26)	0.53 (0.04,4.13)	1.15 (0.1,13.63)	0.42 (0.05,2.57)	1.33 (0.1,13.14)	0.93 (0.08,8.82)	0.57 (0.17,1.59)	1.67 (0.11,23.74)	1.02 (0.19,4.76)	2.92 (0.35,24.65)	**high Balsalazide**

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places. Numbers in red are relative risks obtained based on direct evidence.

Figure 298: Median hazard ratio compared to placebo for treatments based on the outcome of relapse



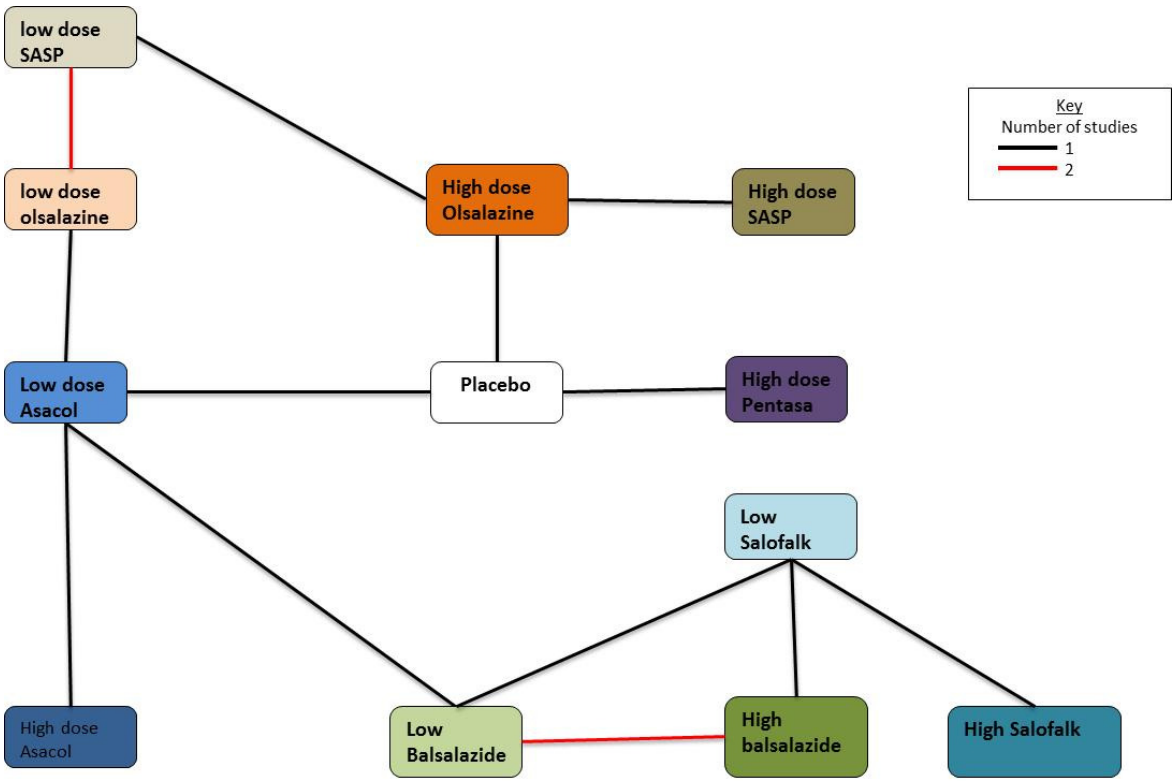
	high Salofalk	high SASP	low SASP	high Olsalazine	high Balsalazide	low Salofalk	low Olsalazine	low Balsalazide	high Asacol	high Pentasa	low Asacol
Median Hazard Ratio	0.11	0.17	0.22	0.25	0.28	0.29	0.31	0.5	0.54	0.63	0.7
Lower 95% CI	0.01	0.04	0.08	0.09	0.04	0.04	0.12	0.11	0.15	0.15	0.26
Upper 95% CI	1.37	0.78	0.54	0.67	2.09	2.7	0.76	2.71	1.66	2.53	1.93

Bold horizontal line denotes the line of no effect.

3.3.2 Network 2: Withdrawals

A total of 13 studies from the original evidence review met the inclusion criteria and reported withdrawals. Figure 299 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown on page 187 alongside their reason(s) for exclusion.

Figure 299: Network for the proportion of people withdrawing from treatment (baseline NMA)



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

There were nine double blind studies, two single blind studies and two with unclear blinding. 11 studies had an unclear method of randomisation, allocation concealment or both. In four studies, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. Three studies included young people in their inclusion criteria, 16-78 years, 15-77 years and 17-75 years.

The trial data from the 13 studies included in the NMA for the proportion of people withdrawing from treatment are presented in Table 9.

Table 26: Study data for the network of the proportion of people withdrawing from treatment

Study	Comparator 1	Comparator 2	Comparator 3	Comparator 1		Comparator 2		Comparator 3	
				Event No.	N	Event No.	N	Event No.	N
Miner 1995	Placebo	Pentasa (4g)	NA	41	102	20	103	NA	NA
Adrizzone 1999c	Placebo	Asacol (1.2g)	NA	7	58	11	54	NA	NA
Wright 1993	Placebo	Olsalazine (2g)	NA	5	52	12	49	NA	NA
Courtney 1992	Asacol (1.2g)	Olsalazine (1g)	NA	10	50	8	49	NA	NA
Paolezi 2005	Asacol (1.2g)	Asacol (2.4g)	NA	8	76	8	80	NA	NA
Green 1998A	Asacol (1.2g)	Balsalazide (3g)	NA	9	50	13	49	NA	NA
Rijk 1982	Olsalazine (2g)	SASP (4g)	NA	8	23	4	23	NA	NA
Ireland 1988	Olsalazine (1g)	SASP (2g)	NA	19	82	11	82	NA	NA
Nilsson 1995	Olsalazine (1g)	SASP (2g)	NA	14	161	17	161	NA	NA
Green 1992	Balsalazide (3g)	Balsalazide (6g)	NA	10	54	7	54	NA	NA
Kruis 2001	Balsalazide (3g)	Balsalazide (6g)	Salofalk (1.5g)	21	48	6	40	15	44
Kruis 2011	Salofalk (1.5g)	Salofalk (3g)	NA	17	212	24	217	NA	NA
Kruis 1995	Olsalazine (2g)	SASP (2g)	NA	5	34	4	40	NA	NA

Table 27 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).
None of the treatments compared in the NMA demonstrated a significant difference in withdrawals compared to placebo.

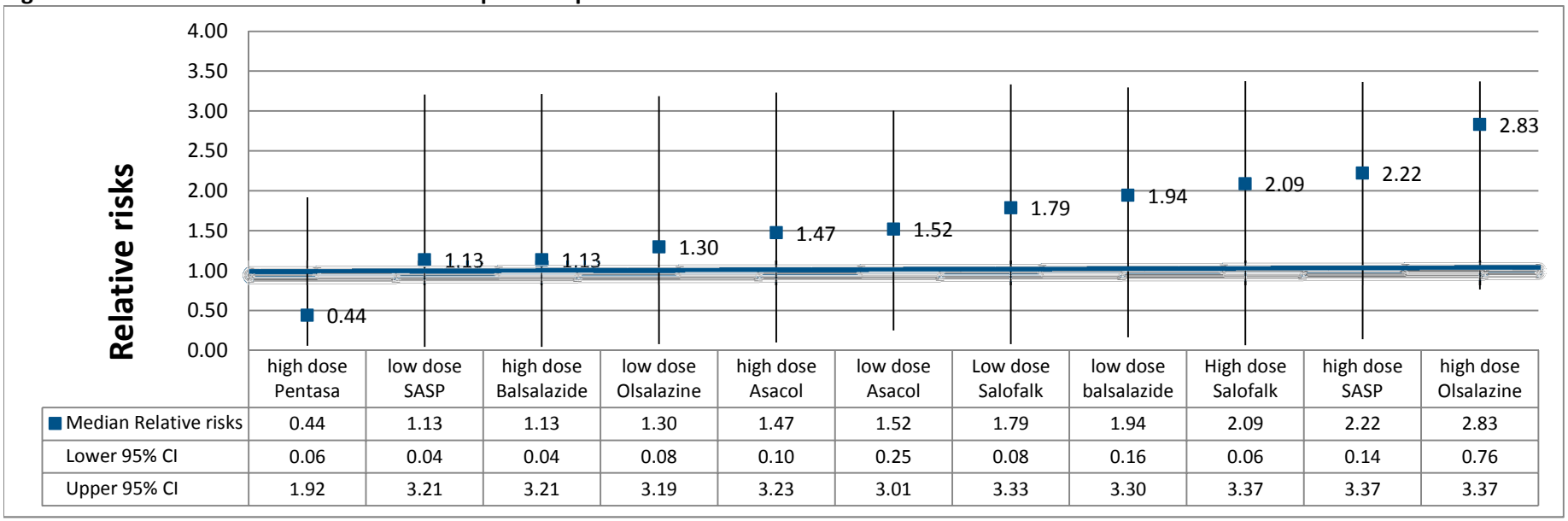
No inconsistency was found between the results of the direct and this network meta-analysis. No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).The median hazard ratio of all treatments compared to placebo is shown in Figure 300. It shows the overlapping confidence intervals of the different treatments.

Table 27: Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people withdrew from treatment

Placebo	**0.48 [0.31, 0.76]**		3.50 [0.95,12.90]		1.69 [0.71, 4.04]						
0.56 (0.06, 1.93)	High Pentasa										
1.54 (0.26,3.02)	6.4 (0.35,28.53)	Low Asacol		0.82 [0.35, 1.89]	0.95 [0.38, 2.40]	1.47 [0.69, 3.13]					
2.63 (0.78,3.38)	10.79 (0.98,46.1)	2.83 (0.47,10.3)	High Olsalazine					0.50 [0.17, 1.43]			
1.4 (0.08,3.2)	5.85 (0.14,27.18)	0.96 (0.14,2.42)	0.68 (0.04,2.1)	Low Olsalazine			0.85 [0.53, 1.36]				
1.51 (0.1,3.23)	6.32 (0.16,29.08)	1.05 (0.17,2.61)	0.74 (0.04,2.25)	2.26 (0.15,9.09)	High Asacol						
1.87 (0.18,3.29)	7.68 (0.29,33.87)	1.37 (0.3,3.31)	0.9 (0.08,2.65)	3 (0.27,12.09)	2.59 (0.25,10.08)	Low balsalazide			**0.47 [0.26, 0.84]**	0.78 [0.46,1.3]	
1.29 (0.05,3.22)	5.45 (0.08,26.21)	0.89 (0.07,2.52)	0.63 (0.02,2.01)	0.96 (0.25,2.09)	1.86 (0.07,6.5)	1.07 (0.05,3.71)	Low SASP				
2.07 (0.15,3.37)	8.54 (0.24,38.09)	2.24 (0.1,8.52)	0.77 (0.11,1.3)	8.44 (0.11,24.79)	5.61 (0.1,20.82)	3.51 (0.08,11.08)	20.32 (0.12,42.71)	High SASP			
1.27 (0.05,3.21)	5.49 (0.09,26.1)	0.89 (0.08,2.52)	0.62 (0.02,2.03)	1.96 (0.07,8.09)	1.73 (0.07,6.66)	0.65 (0.14,1.24)	3.8 (0.08,14.48)	2.3 (0.03,9.19)	High balsalazide	2.27 [0.98,5.2]	
1.74 (0.09,3.33)	7.26 (0.15,32.51)	1.31 (0.13,3.71)	0.83 (0.04,2.55)	2.96 (0.13,12.12)	2.79 (0.12,10.06)	1.00 (0.21,2.29)	5.77 (0.14,21.72)	3.08 (0.05,12.46)	2.05 (0.45,7.01)	Low Salofalk	1.38 [0.76, 2.49]
1.94 (0.07,3.38)	7.98 (0.13,35.82)	1.54 (0.1,4.61)	0.94 (0.03,2.78)	3.66 (0.1,14.62)	3.34 (0.09,12.31)	1.25 (0.13,3.45)	7.3 (0.11,25.77)	3.41 (0.04,13.2)	2.88 (0.28,11.01)	1.32 (0.29,3.4)	High Salofalk

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

Figure 300: Median relative risk ratio compared to placebo for treatments based on the outcome of withdrawals



	high dose Pentasa	low dose SASP	high dose Balsalazide	low dose Olsalazine	high dose Asacol	low dose Asacol	Low dose Salofalk	low dose balsalazide	High dose Salofalk	high dose SASP	high dose Olsalazine
Median Relative risks	0.44	1.13	1.13	1.30	1.47	1.52	1.79	1.94	2.09	2.22	2.83
Lower 95% CI	0.06	0.04	0.04	0.08	0.10	0.25	0.08	0.16	0.06	0.14	0.76
Upper 95% CI	1.92	3.21	3.21	3.19	3.23	3.01	3.33	3.30	3.37	3.37	3.37

Bold horizontal line denotes the line of no effect

3.4 Combined NMA results

The GDG reviewed the results of the baseline NMA and considered that there were no clinically significant differences between the low dose oral ASAs. This was the same for the high dose oral ASAs. A dose effect was not observed between lower and higher doses of ASAs but in the clinical review a dose relationship was suggested. It was thought that the same groupings should be used as in the induction NMAs because the event rates are so small and there is large uncertainty so grouping them in low and high doses may strengthen the power to demonstrate an effect.

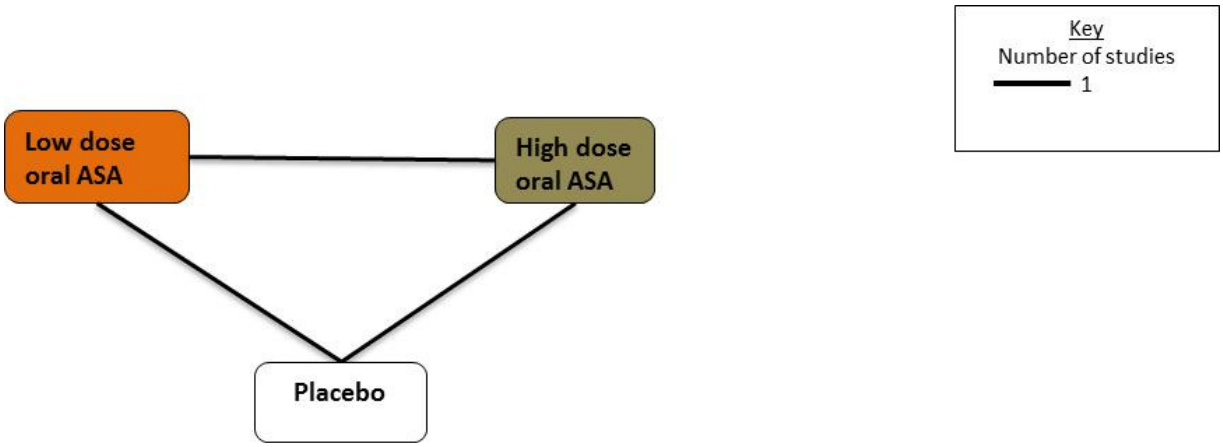
Based on this, a second NMA (combined NMA) was conducted to inform the health economic model. This combined all low dose ASAs into one treatment group, and all high dose ASAs into another treatment group. The two networks for the combined NMA are described below.

Network 1: Relapses

Five studies[22,42,58,98,113] which were included in the baseline analysis were excluded as they compared the same dose ranges of ASAs for example, a low dose versus a low dose or a high dose versus a high dose. The methodology described in section 3.2.4 was used. The network is shown in Figure 301.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

Figure 301: Network for the proportion of people having a relapse (combined NMA)



The results are presented in Table 28 and Table 29 along with the results of the individual treatments.

Table 28: Hazard ratio of low dose oral ASA versus placebo

Drug	Hazard ratio from Baseline NMA (95% CI)	Hazard ratio from combined NMA (95% CI)
Low dose Salofalk	0.29 (0.04, 2.7)	0.49 (0.24, 0.93)
Low dose Asacol	0.70 (0.26, 1.93	
Low dose SASP	0.22 (0.08, 0.54)	
Low dose Olsalazine	0.31 (0.12, 0.76)	
Low dose Balsalazide	0.50 (0.11, 2.71)	

Table 29: Hazard ratio of high dose oral ASA versus placebo

Drug	Hazard ratio from Baseline NMA (95% CI)	Hazard ratio from combined NMA (95% CI)
High dose Salofalk	0.11(0.01, 1.37)	0.36 (0.18, 0.67)
High dose Asacol	0.54(0.15, 1.66)	
High dose SASP	0.17(0.04, 0.78)	
High dose Olsalazine	0.25(0.09, 0.67)	
High dose Balsalazide	0.28(0.04, 2.09)	

Network 2: Withdrawals

Five studies[22,42,58,98,113] which were included in the baseline analysis NMA were excluded as they compared the same dose ranges of ASAs for example, a low dose versus a low dose or a high dose versus a high dose. The methodology described in section 3.2.4 was used. The network is shown in Figure 302.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The output from the NMA was odds ratios to aid calculations in the maintenance of remission health economic model. The results are shown in Table 30 and Table 31 along with the results of the individual treatments.

Figure 302: Network for the proportion of people withdrawing from treatment (combined NMA)

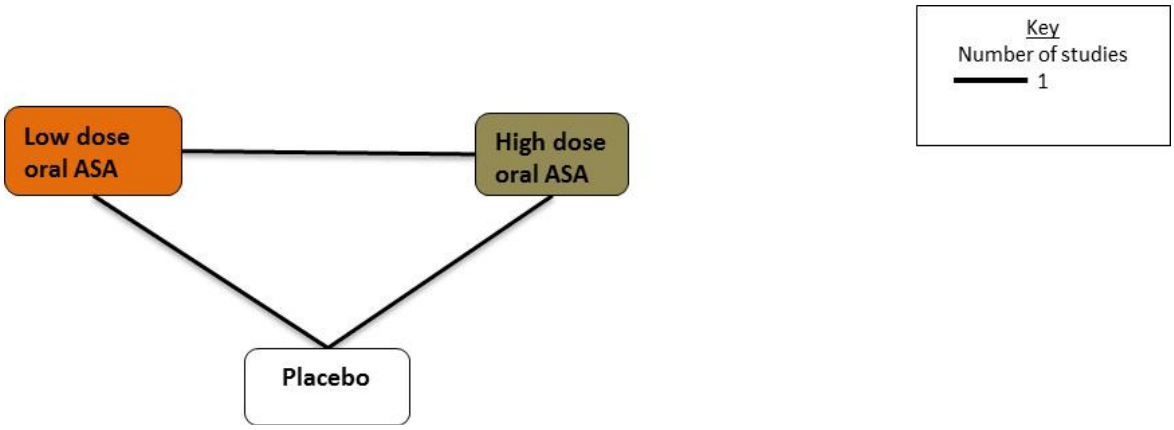


Table 30: odds ratio of low dose oral ASA versus placebo

Drug	Odds ratio from Baseline NMA (95% CI)	Odds ratio from combined NMA (95% CI)
Low dose Salofalk	1.79 (0.08, 3.33)	1.71(0.34,11.4)
Low dose Asacol	1.52 (0.25, 3.01)	
Low dose SASP	1.13 (0.04, 3.21)	
Low dose Olsalazine	1.30 (0.08, 3.19)	
Low dose Balsalazide	1.94 (0.16, 3.30)	

Table 31: odds ratio of high dose oral ASA versus placebo

Drug	Odds ratio from Baseline NMA (95% CI)	Odds ratio from combined NMA (95% CI)
High dose Salofalk	2.09 (0.06, 3.37)	1.18(0.27,7.08)
High dose Asacol	1.47 (0.10, 3.23)	
High dose SASP	2.22 (0.14, 3.37)	

Drug	Odds ratio from Baseline NMA (95% CI)	Odds ratio from combined NMA (95% CI)
High dose Olsalazine	2.83 (0.76, 3.37)	
High dose Balsalazide	1.13 (0.04, 3.21)	

3.5 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 7 and Appendix H, deciding upon the most effective intervention for the maintenance of remission of people with mild to moderate left sided or extensive ulcerative colitis is difficult. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons, NMA of the direct evidence were performed by preserving the trial randomization and minimizing bias.

Our analysis was based on a total of 18 studies of 12 different interventions. The studies formed a network for each outcome.

The findings from the NMA will be used to facilitate the GDG in decision making when developing recommendations for the maintenance of remission in people with left sided or extensive ulcerative colitis and as a base for the cost-effectiveness analysis.

Baseline NMA

In the first network of rate of relapse, low and high doses of Olsalazine and low and high doses of Sulfasalazine were significantly more effective than placebo. However, the ranking of these treatments for median relative risks need to be interpreted with caution due to the overlapping of their confidence intervals of the treatments.

In the second network of withdrawals, none of the treatments were significant compared to either placebo or each other.

Combined NMA

In the first network, high dose ASA was more effective than either low dose ASA or placebo. In the second network, there was a higher probability of withdrawing from low dose ASA than from high dose ASA.

In summary, the NMA analysis focused on two of the important clinical outcomes for assessing efficacy of medical treatments in maintaining remission. The results should be interpreted with caution due to several limitations of the analysis as described below.

Limitations:

- Almost all comparisons were based on single studies.
- A few of the comparisons were small studies (large confidence intervals).
- Poor quality studies.
- The use of SASP tolerant populations in trials could favour the efficacy of SASP compared to other ASAs.
- Varying times in remission prior to enrolling in trial could bias the results.
- Many of the studies did not give a breakdown of the extent of the disease and are at risk of being an indirect population.
- Use of different indexes for remission.
- The definition of low and high doses may influence the efficacy of treatments depending on what group they fall into.

- As with all meta-analyses, the studies available for analysis could be influenced by publication bias; however, no standardized methods have been fully developed to assess this type of bias in an NMA.

3.6 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the clinical reviews for the maintenance of remission of adults with mild to moderate left sided/ extensive ulcerative colitis even when direct comparative data was lacking.

Low and high doses Olsalazine and low and high doses of Sulphasalazine were significantly better than placebo in maintaining remission. The superiority of one drug over another drug could be determined, however, high doses of oral ASA were better than low doses of oral ASA. In terms of withdrawals, the superiority of one drug over another drug could be determined.

3.7 Appendices

3.7.1 Excluded studies

3.7.1.1 Baseline NMA

Table 32: Studies from the direct clinical evidence review which were excluded from the NMA

Study	Reason for exclusion
BARDAZZI1994[6]	Regimen comparison
DALBASIO1997[24]	Rectal preparations are excluded
DHAENS2012[26]	Dose and regimen comparison
DIGNASS2009[31]	Mesalazine comparison
HAWKEY1997[54]	No outcomes
ITO2010B[59]	Regimen comparison
KAMM2008[64]	MEZAVANT XL 4.8g is excluded
KANE2003[67]	Regimen comparison
KANE2008[66]	Dose and regimen comparison
KILLERICH1992[68]	<50% left sided or extensive disease
MISIEWICZ1965[92]	One treatment arm <50% left sided or extensive disease
PRANTERA2009[106]	Mesalazine comparison
RIIS1973[111]	Mixed sulphasalazine dose (2-6 tablets). Unclear dosing and can't separate out.
RILEY1988A[114]	<50% left sided or extensive disease
SANDBORN2010[120]	Dose and regimen comparison
YOKOYAMA2007[138]	Rectal preparations are excluded

3.7.1.2 Combined NMA

Study	Reason for exclusion
COURTNEY1992[22]	Low dose versus low dose aminosalicylate
GREEN1998A[42]	Low dose versus low dose aminosalicylate
IRELAND1988[58]	Low dose versus low dose aminosalicylate

Study	Reason for exclusion
NILSSON1995[98]	Low dose versus low dose aminosalicylate
RIJK1992[113]	High dose versus high dose aminosalicylate

3.7.2 WinBUGs codes

3.7.2.1 Relapse: random effects model

```
model{
#Define Prior Distributions
#on random tx effect variance
sd~dunif(0,5)
reTau < - 2/pow(sd,2)
#On tx effect mean
beta[1] < -0
for (tt in 2:nTx){
beta[tt]~dnorm(0,1.0E-6)
}
#On individual study baseline effect
for(ss in 1:nStudies){
alpha[ss] ~ dnorm(0,1.0E-6)
}
#Define random effect
for (ss in 1:nStudies){
for(tt in 1:nTx){
re[ss,tt]~dnorm(0,reTau)
}
}
#Fit data
#For hazard ratio reporting studies
for(ii in 1:LnObs ){
Lmu[ii] < - alpha[Lstudy[ii]]*multi[ii] + re[Lstudy
[ii],Ltx[ii]] -
re[Lstudy[ii],Lbase[ii]] + beta[Ltx[ii]] - beta
[Lbase[ii]]
Lprec[ii] < - 1/pow(Lse[ii],2)
Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
}
#For binary data reporting studies
for(ss in 1:BnObs){
logCumHaz[ss] < - alpha[Bstudy[ss]] + re[Bstudy
[ss],Btx[ss]] -
re[Bstudy[ss],Bbase[ss]] + beta[Btx[ss]] - beta
[Bbase[ss]]
cumFail[ss] < - 1-exp(-1*exp(logCumHaz[ss]))
Br[ss] ~ dbin(cumFail[ss], Bn[ss])
}
# Calculate HRs
for (hh in 2:nTx) {
hr[hh] < -exp(beta[hh])
}
# Ranking plot
for (ll in 1:nTx) {
for (mm in 1:nTx) {
rk[ll,mm] < - equals(ranked(beta[],mm),beta[ll])
}
```

```
}
}

# Data as for fixed effects analysis
############################
# Initial values
list(alpha = c(-0.50,-0.50,-0.50,-0.50,-0.50), beta =
c(NA,-0.5,-0.5,-0.5),sd = 0.1)
list(alpha = c(0.50,0.50,0.50,0.50,0.50), beta = c

(NA,0.5,0.5,0.5),sd = 1)
```

3.7.2.2 Withdrawals: random effects model

```
model{

for (i in 1:NS)

{

Events[i] <- r[i,1]*equals(t[i,1],1)

Numpatients[i] <- n[i,1]*equals(t[i,1],1)

}

totEvents<-sum(Events[])

totNumpatients<-sum(Numpatients[])

BR<- totEvents/totNumpatients

for(i in 1:NS){

w[i,1] < -0

delta [i,t[i,1]] < -0

mu[i] ~ dnorm(0,.0001)

for (k in 1:na[i])  {

r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])

logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]

rhat[i,k] <- p[i,t[i,k]] * n[i,k]

dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

}

sdev[i]<- sum(dev[i,1:na[i]])

for (k in 2:na[i]) {

delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]

taud [i,t[i,k]] < -tau * 2 * (k - 1) / k
```

```
w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])

sw[i,k] <-sum(w[i,1:k-1])/(k-1) }

}

d [1] <- 0

for (k in 2:NT){d[k] ~ dnorm(0,.0001) }

sd~dunif(0,2)

tau<-1/pow(sd,2)

rr [1] < -1

for (k in 2:NT)  {logit(v[k])<-logit(BR)+d[k]

rr[k]<-v[k]/BR

T[k]<-v[k]/BR}

sumdev <- sum(sdev[])

for (k in 1:NT) {

rk[k]<-NT+1-rank(rr[],k)

best[k]<-equals(NT+1-rank(rr[],k),1)}

for (c in 1:(NT-1))

{  for (k in (c+1):NT)

{  lor[c,k] <- d[k] - d[c]

log(or[c,k]) <- lor[c,k]

lrr[c,k] <- log(rr[k]) - log(rr[c])

log(rrisk[c,k]) <- lrr[c,k] } } }
```

3.7.3 Treatment codes

3.7.3.1 Baseline NMA: Relapse

1. Placebo
2. High Pentasa
3. high Asacol
4. high Olsalazine
5. Low Asacol
6. Low SASP
7. Low Olsalazine
8. Low Balsalazide
9. High SASP
10. Low Salofalk
11. High Salofalk

12.High Balsalazide

3.7.3.2 Baseline NMA: Withdrawals

1. Placebo
2. High Pentasa
3. high Asacol
4. high Olsalazine
5. Low Olsalazine
6. High Asacol
7. Low Balsalazide
8. Low SASP
9. High SASP
10. High Balsalazide
11. Low Salofalk
12. High Salofalk

3.7.3.3 Combined NMA: Relapse

13.Placebo
14.High dose ASA
15.Low dose ASA

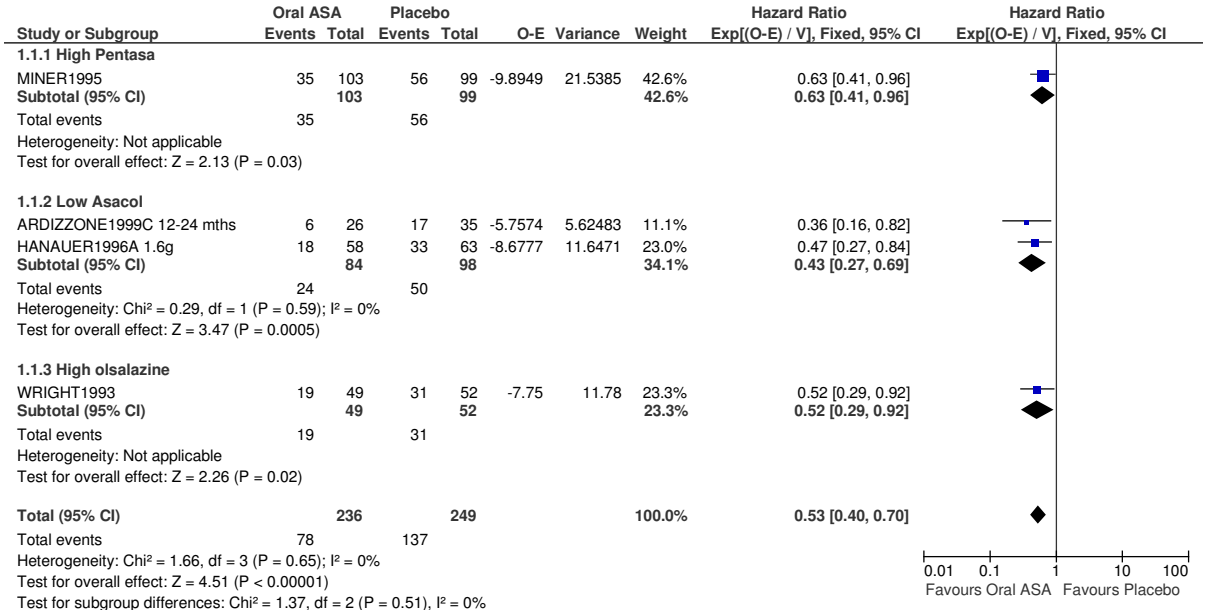
3.7.3.4 Combined NMA: Withdrawals

16.Placebo
17.Low dose ASA
18.High dose ASA

3.7.4 Forest plots

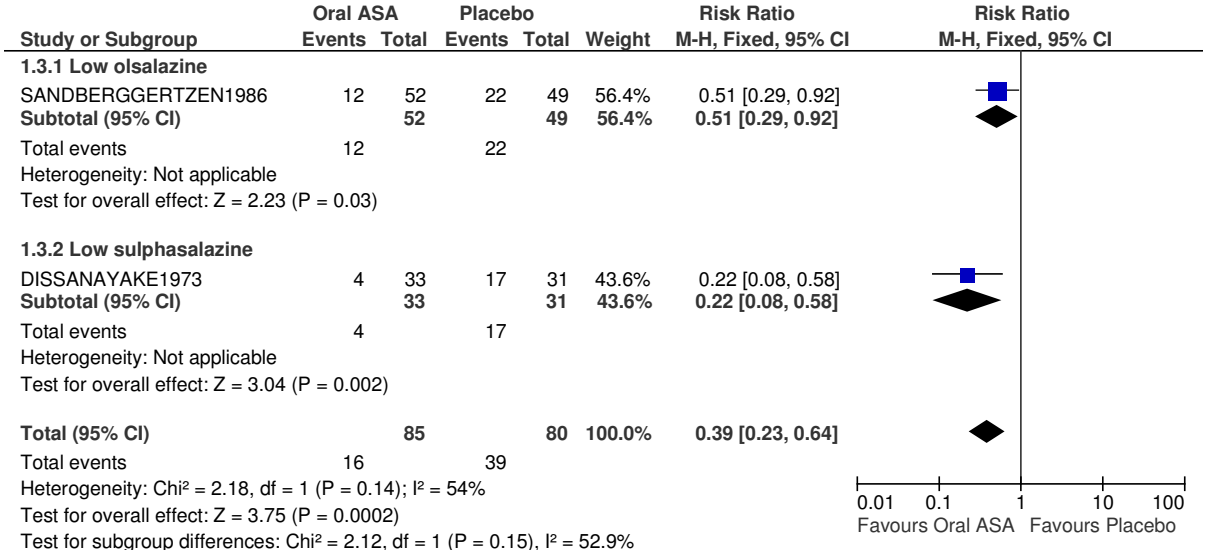
3.7.4.1 Oral Aminosalicylates versus placebo

Figure 303: Relapse (HR)



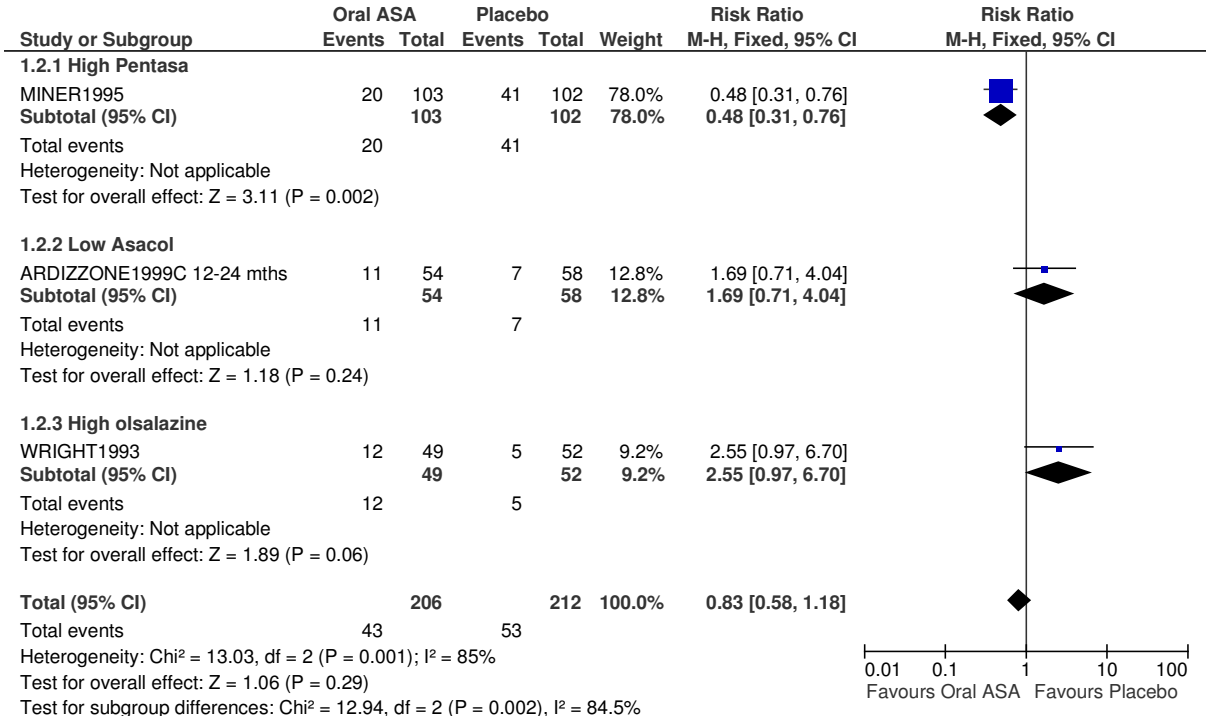
Source: <Insert Source text here>

Figure 304: Relapse (RR)



Source: <Insert Source text here>

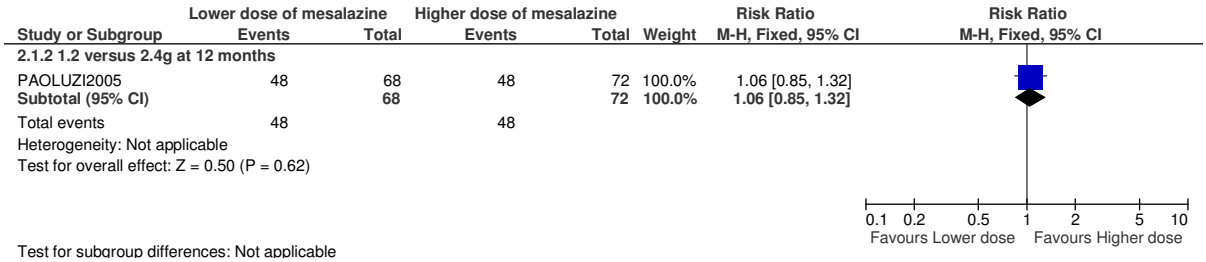
Figure 305: Withdrawals



Source: <Insert Source text here>

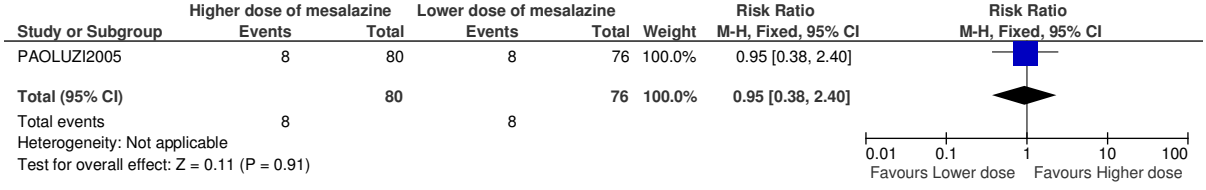
3.7.4.2 Asacol dose comparison

Figure 306: Relapse (RR) – low versus high dose



Source: <Insert Source text here>

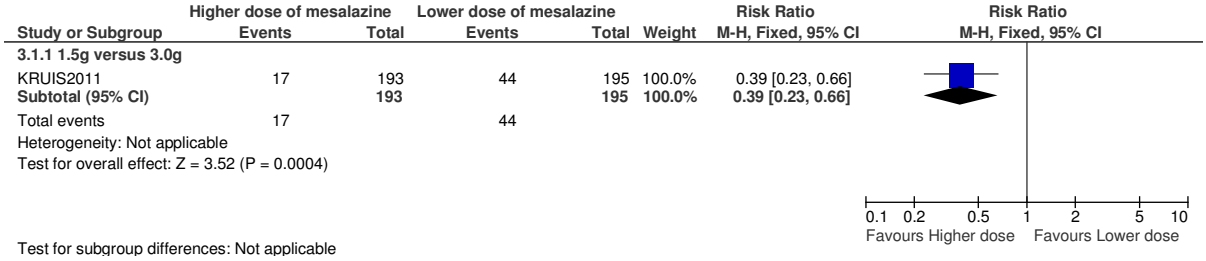
Figure 307: Withdrawals



Source: <Insert Source text here>

3.7.4.3 Salofalk dose comparison

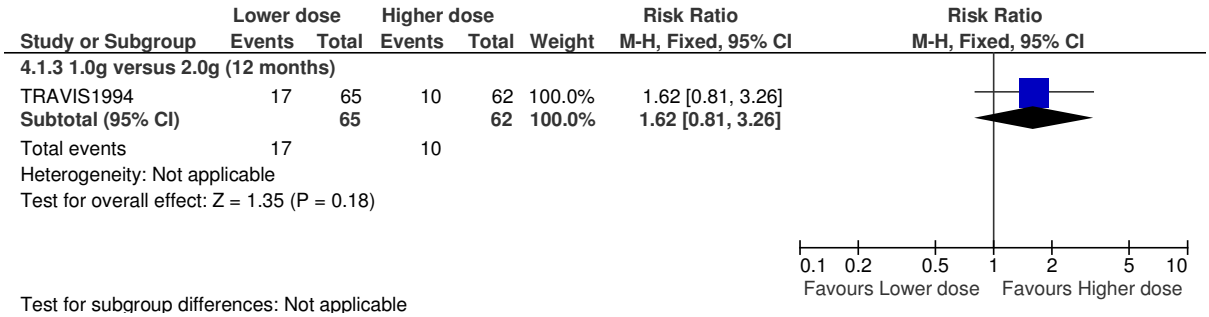
Figure 308: Relapse (HR) – high versus low dose



Source: <Insert Source text here>

3.7.4.4 Olsalazine dose comparison

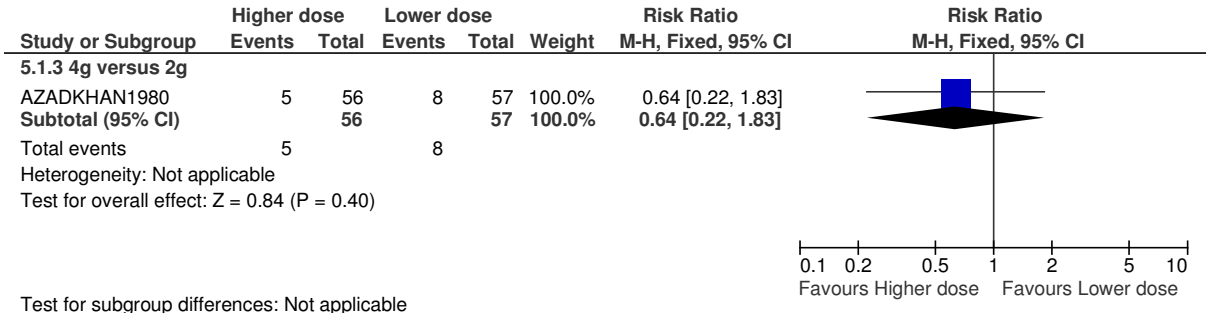
Figure 309: Relapse (RR) – low versus high dose



Source: <Insert Source text here>

3.7.4.5 Sulphasalazine dose comparison

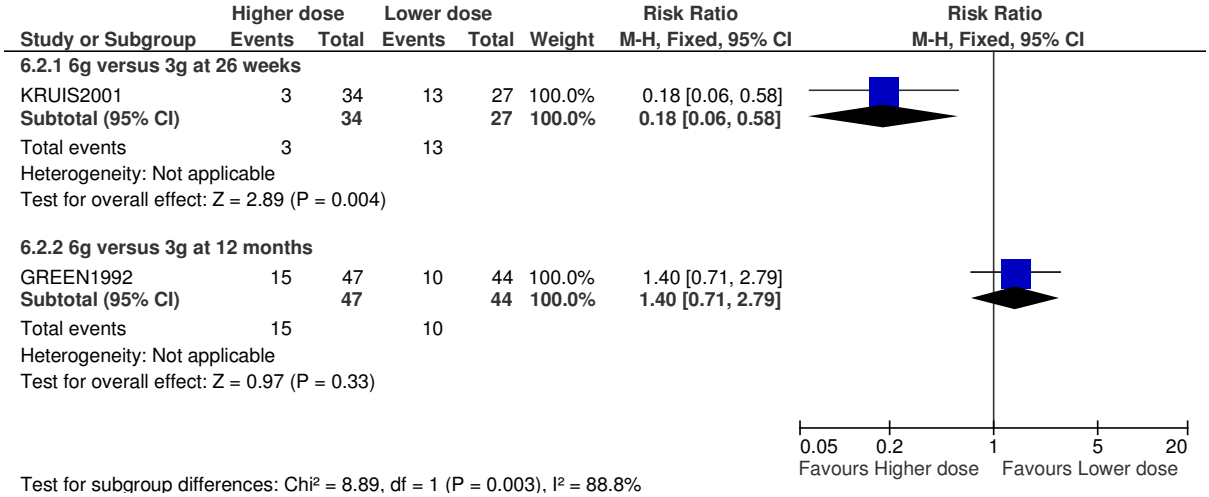
Figure 310: Relapse (RR) – high versus low dose



Source: <Insert Source text here>

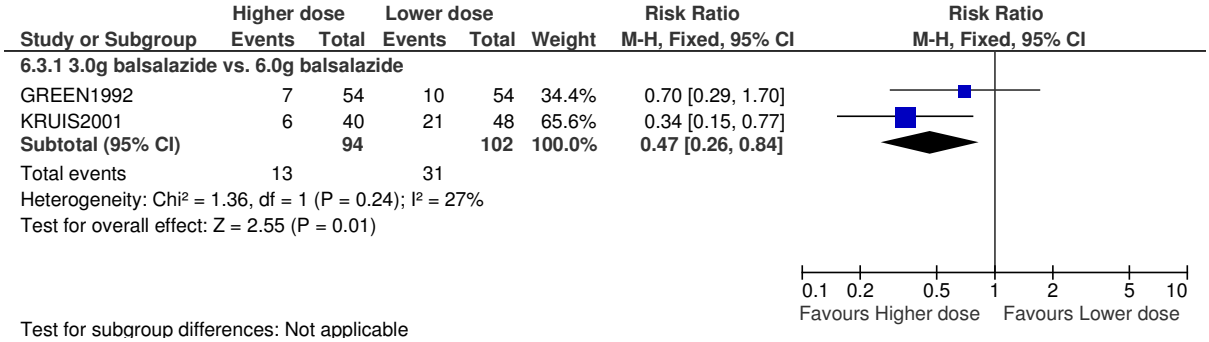
3.7.4.6 Balsalazide dosing

Figure 311: Relapse (RR) – high versus low dose



Source: <Insert Source text here>

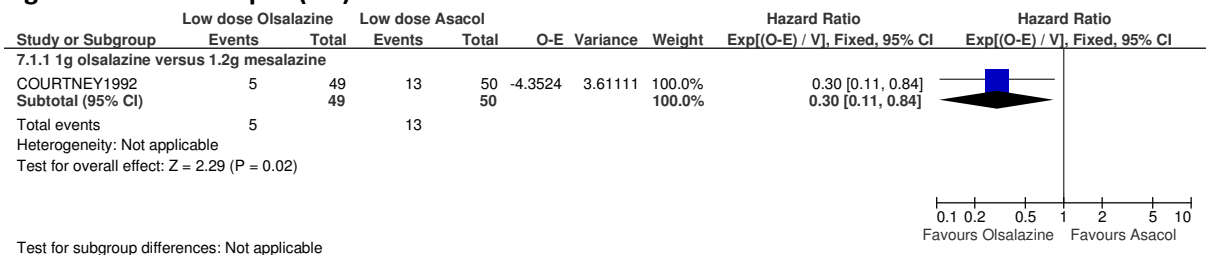
Figure 312: Withdrawals – high versus low



Source: <Insert Source text here>

3.7.4.7 Low dose olsalazine versus low dose Asacol

Figure 313: Relapse (HR)



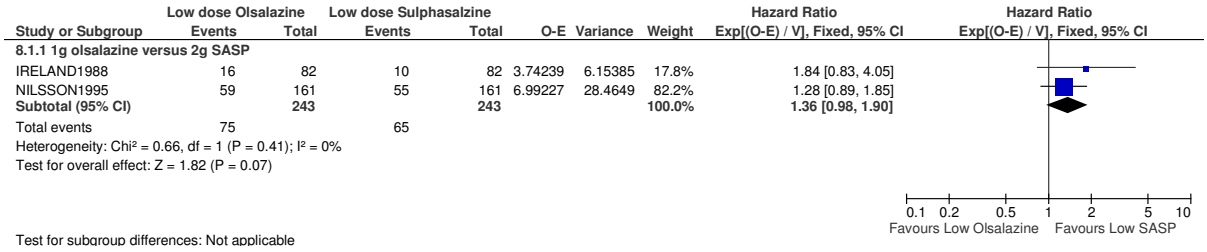
Source: <Insert Source text here>

Figure 314: Withdrawals

Source: <Insert Source text here>

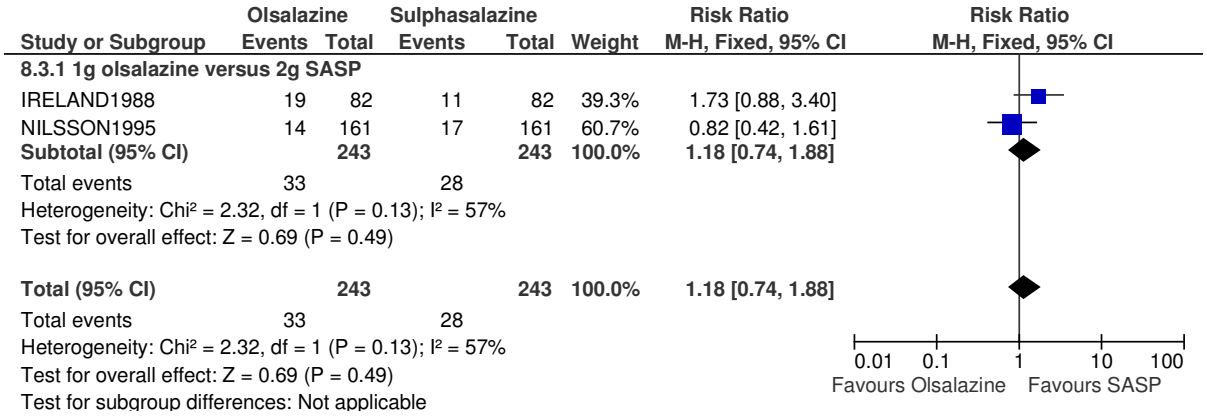
3.7.4.8 Low dose olsalazine versus low dose sulphasalazine

Figure 315: Relapse (HR)



Source: <Insert Source text here>

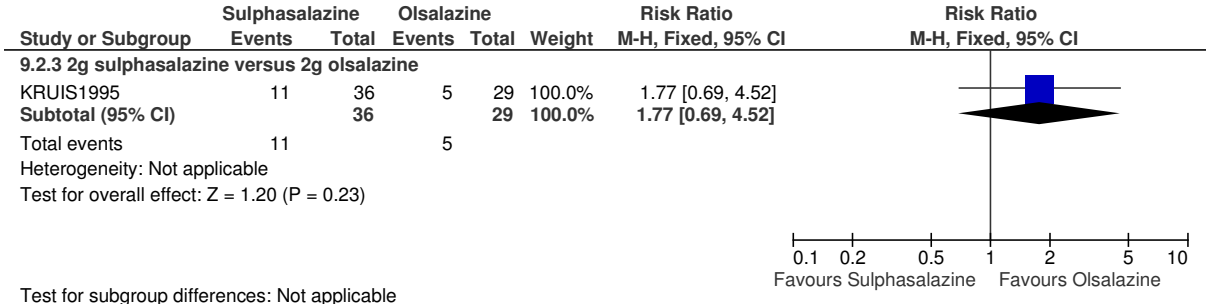
Figure 316: Withdrawals



Source: <Insert Source text here>

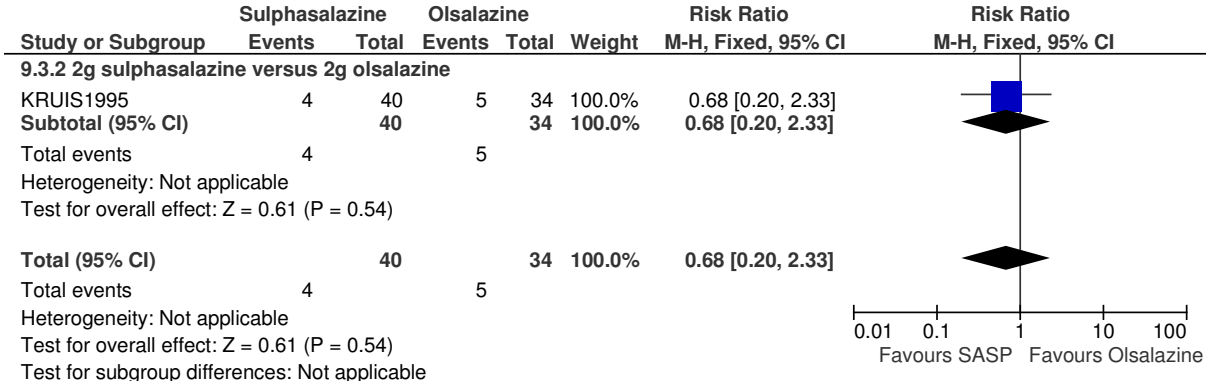
3.7.4.9 Low dose sulphasalazine versus high dose olsalazine

Figure 317: Relapse (RR)



Source: <Insert Source text here>

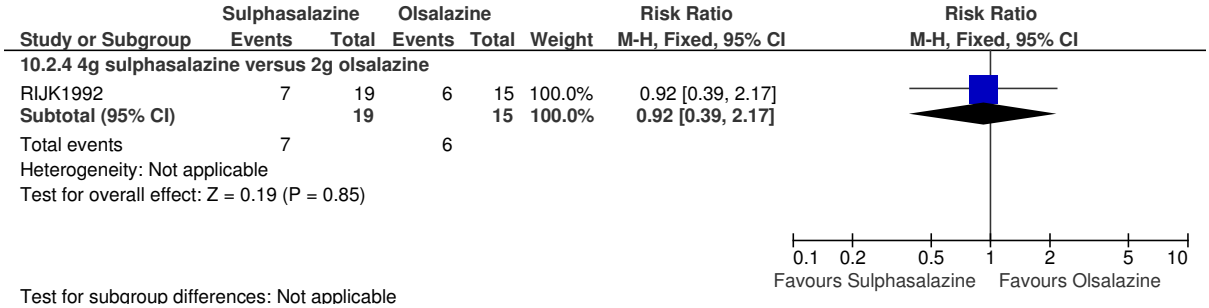
Figure 318: Withdrawals



Source: <Insert Source text here>

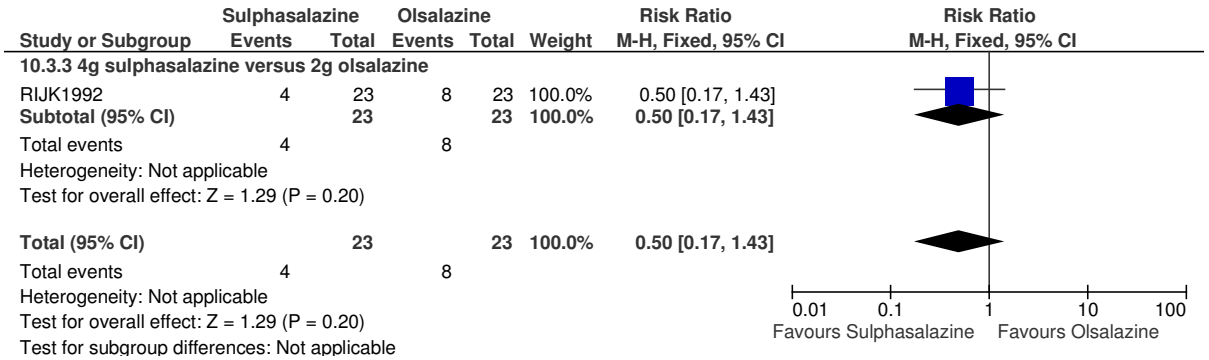
3.7.4.10 High dose sulphasalazine versus high dose olsalazine

Figure 319: Relapse (RR)



Source: <Insert Source text here>

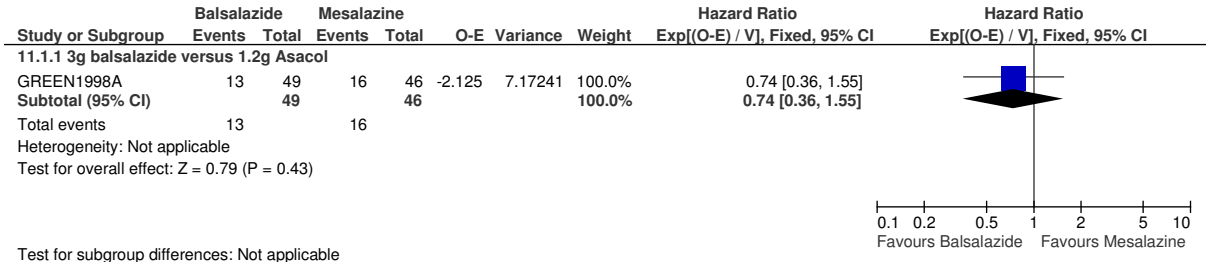
Figure 320: Withdrawals



Source: <Insert Source text here>

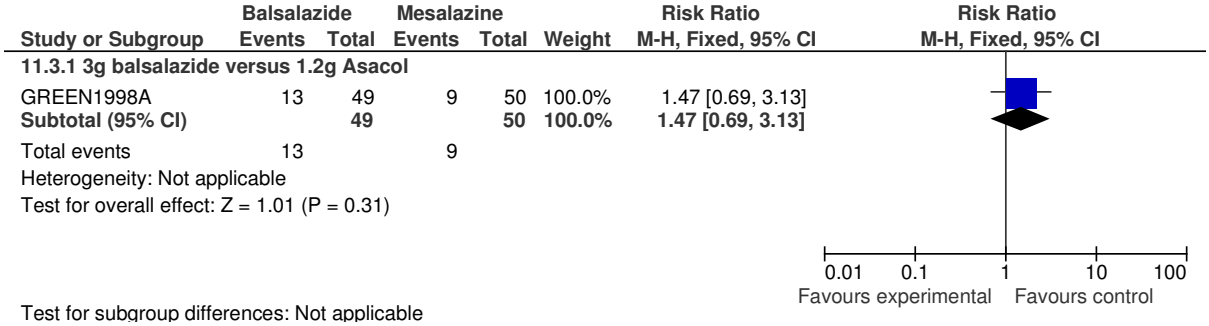
3.7.4.11 Low balsalazide versus low Asacol

Figure 321: Relapse (HR)



Source: <Insert Source text here>

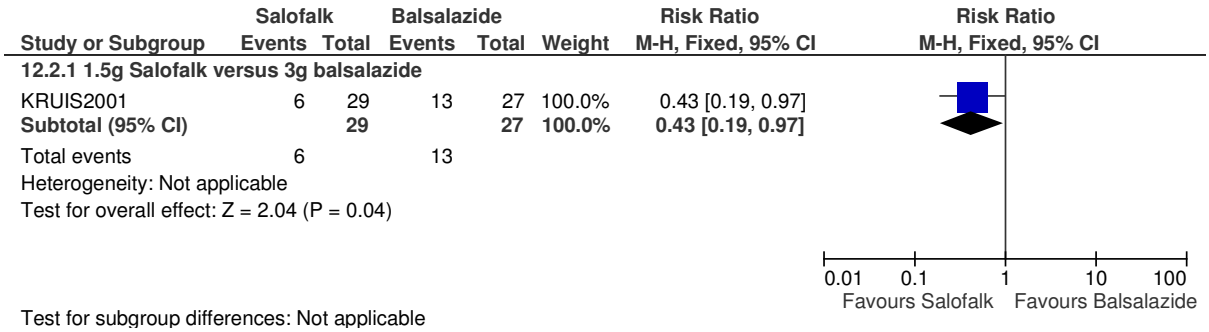
Figure 322: Withdrawals



Source: <Insert Source text here>

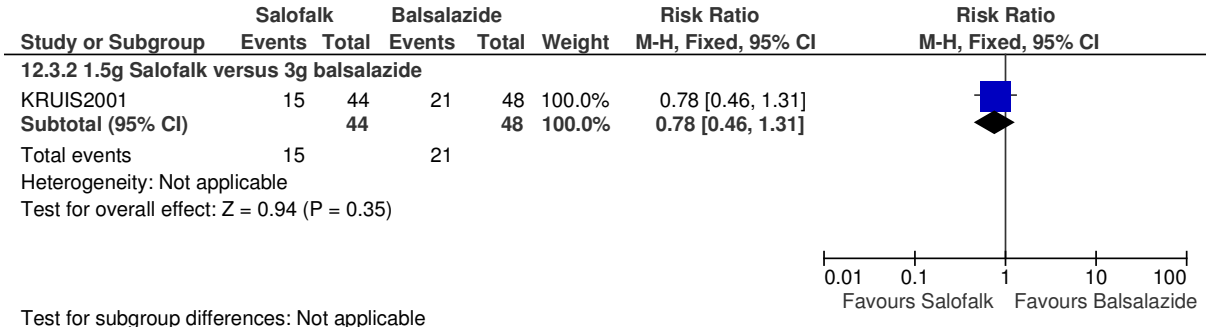
3.7.4.12 High Salofalk versus low balsalazide

Figure 323: Relapse (RR)



Source: <Insert Source text here>

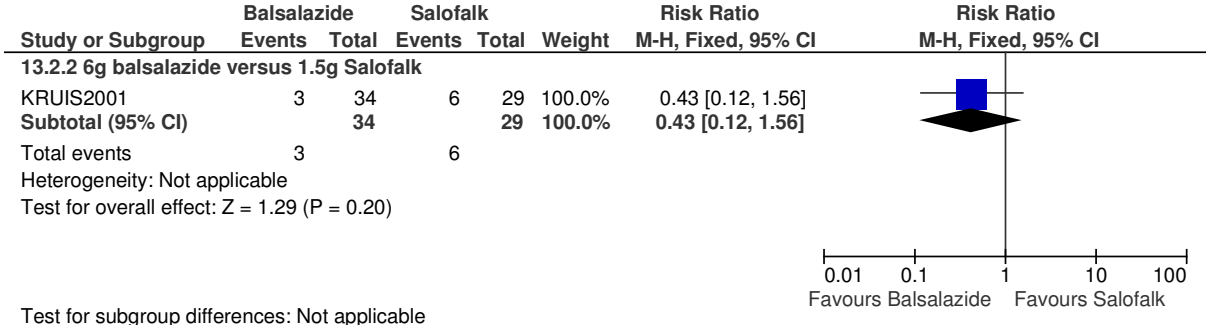
Figure 324: Withdrawals



Source: <Insert Source text here>

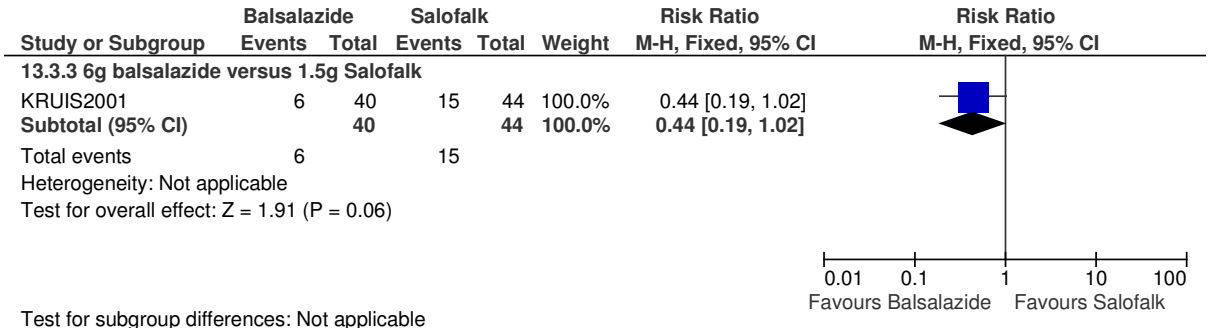
3.7.4.13 High balsalazide versus high Salofalk

Figure 325: Relapse (RR)



Source: <Insert Source text here>

Figure 326: Withdrawals



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4 Appendix K: Costs of drugs used in the treatment of ulcerative colitis

The costs of drugs reviewed in the guideline are presented below.

Table 33: Costs of topical aminosalicylates

Drug	Form	Strength	Pack size	Cost per pack	Unit costs
Asacol	suppositories	250mg	20	£4.82	£0.24
Asacol	suppositories	500mg	10	£4.82	£0.48
Asacol	foam enema	1g/metered application	14 applications	£26.72	£1.91
Pentasa	suppositories	500mg	28	£40.01	£1.43
Pentasa	retention enema	1g/100mL	28	£17.73	£0.63
Salazopyrin	suppositories	500mg	10	£3.30	£0.33
Salofalk	suppositories	500mg	30	£14.81	£0.49
Salofalk	enema	2g/59mL	7	£29.92	£4.27
Salofalk	rectal foam	1g/metered application	14 applications	£30.17	£2.16

Source: BNF 61[63]

Table 34: Costs of topical corticosteroids

Drug	Form	Strength	Pack size	Cost per pack	Unit costs
Budenofalk	rectal foam	2 mg budenoside/metered application	14 applications	£57.11	£4.08
Entocort	enema	2 mg budenoside/100 mL	7	£39.60	£4.71
Hydrocortisone	foam	hydrocortisone acetate 10%	14 applications	£9.33	£0.66
Prednisolone	rectal foam	20mg prednisolone /metered application,	14 applications	£48.00	£3.43
Predsol	retention enema	20mg prednisolone /100-mL	7	£7.50	£1.07
Predsol	suppositories	prednisolone 5 mg	10	£1.35	£0.14

Source: BNF 61[63]

Table 35: Costs of oral corticosteroids

Drug	Form	Strength	Pack size	Cost per pack	Unit costs
Beclometasone	tablets	5mg	30	£56.56	£1.89
Prednisolone	tablets	5mg	28	£0.96	£0.05
Prednisolone	enteric coated tablets	5mg	28	£3.79	£0.17

Source: *BNF 61*[63]

Table 36: Costs of oral aminosalicylates

Cost item	Form	Strength	Pack size	Cost per pack
Pentasa	SR tablets	500mg	100	£30.74
Pentasa	M/R granules	1g	50	£30.74
Pentasa	M/R granules	2g	60	£73.78
Pentasa	M/R tablets	1g	60	£36.89
Mezavant XL	G/R tablets	1.2g	60	£62.44
Mesalazine	E/C tablets	400mg	120	£41.62
Salofalk	G/R tablets	500mg	100	£32.38
Salofalk	G/R, M/R granules	1.5g	60	£48.85
Salofalk	G/R, M/R granules	500mg	100	£28.74
Salofalk	E/C tablets	250mg	100	£16.19
Asacol	E/C, M/R tablets	400mg	90	£29.41
Asacol	E/C, M/R tablets	800mg	180	£117.62
Sulfasalazine	E/C tablets	500mg	100	£10.14
Sulazine	E/C tablets	500mg	112	£14.83
Sulfasalazine	tablets	500mg	112	£7.83
Salazopyrin En_Tab	E/C tablets	500mg	112	£8.43
Salazopyrin	tablets	500mg	112	£6.97
Dipentum	tablets	500mg	60	£21.18
Dipentum	capsules	250mg	112	£19.77
Balsalazide	capsules	750mg	130	£30.42

Note: *Drugs that have different strengths but the same form and costs have been excluded from this table.*

Source: *BNF 61*[63]

Table 37: Costs of immunomodulators

Cost item	Form	Strength	Pack size	Cost per pack
Azathioprine				
Azathioprine	tablets	25mg	28	£4.41
Azathioprine	tablets	50mg	56	£4.36
Imuran	tablets	25mg	100	£10.99
Imuran	tablets	50mg	100	£7.99
Ciclosporin				

Cost item	Form	Strength	Pack size	Cost per pack
Capimune	capsules	25mg	30	£13.50
Capsorin	capsules	25mg	30	£13.11
Deximune	capsules	25mg	30	£13.80
Neoral	capsules	25mg	30	£18.59
Tacrolimus				
Adoport	capsules	500 micrograms	50	£50.50
Capexion	capsules	500 micrograms	50	£52.50
Modigraf	granules	200 micrograms	50 sachets	£71.30
Prograf	capsules	500 micrograms	50	£61.88
Tacni	capsules	500 micrograms	50	£50.48
Vivadex	capsules	500 micrograms	50	£46.41
Advagraf	M/R capusles	500 micrograms	50	£35.79
Methotrexate				
Methotrexate	tablets	2.5mg	28	£4.61

Source: *BNF 61*[63]

Table 38: Costs of drugs for severe ulcerative colitis

Cost item	Form	Strength	Pack size	Cost per pack
Ciclosporin				
Sandimmun	concentrate for intravenous infusion	50mg/ml	• 1-mL ampoule • 5-mL ampoule	• £1.94 • £9.17
Hydrocortisone				
Solu-Cortef	powder for reconstitution	100mg	one vial	£1.16
Methylprednisolone				
Solu-Medrone	powder for reconstitution	40mg	one vial	£1.58

Source: *BNF 61*[63]

5 Appendix L: Cost-effectiveness analyses

5.1 Induction of remission

5.1.1

Please note that evidence on treatments for inducing remission in people with mild-to-moderate ulcerative colitis was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

Table 39: Relevant economic studies on induction of remission

Study	Description	Comments
Brereton[10]	2.4g/day MEZAVANT XL mesalazine (Mezavant) versus 2.4g/day mesalazine (Asacol)	MEZAVANT XL was found to be more effective and more costly with an incremental cost-effectiveness ratio of £749 per QALY.
Buckland[11]	High dose (4.8g/day) versus standard dose (2.4g/day) mesalazine (Asacol)	High dose is less costly and more effective than standard dose.
Mackowiak[86]	Balsalazide (6.75g/day) versus mesalazine delayed tablets (2.4g/day or 4.8g/day)	Balsalazide dominates mesalazine as it costs less per symptom or steroid free day.
Connolly[19]	Oral mesalazine (4g/day) versus oral mesalazine (4g/day) and mesalazine enema (1g/100ml)	Combination therapy is cheaper and more effective.

These studies help to highlight the cost-effectiveness of specific aminosalicylates (ASAs) or ASA doses. However, other ASAs are available which have not been addressed. In addition, the studies have modelled different treatment sequences after failure of first line treatment. The GDG considered that there are other clinically relevant sequences that have not been captured and hence this topic was considered to be a top priority for original economic analysis. The treatment options available for patients with proctitis and proctosigmoiditis was deemed to be less variable and hence modelling for this subgroup was not identified as high priority by the GDG. The original economic model presented here sought to address the various treatment options available for the induction of remission in people with mild to moderate left sided or extensive ulcerative colitis.

5.1.2 Methods

5.1.2.1 Model overview

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective (PSS).

5.1.2.2 Comparators

The comparators examined in the model are treatment sequences chosen by the GDG. The GDG considered the suitability of the drugs for use in patients with mild to moderate left sided or extensive UC and current clinical practice when compiling the treatment sequences.

Based on the studies reviewed in the induction of remission chapter, two network meta-analyses (NMAs) were conducted addressing the treatments for the induction of remission (Appendix I). A baseline NMA was conducted which addressed three outcomes; clinical remission, clinical improvement and withdrawals due to adverse events. The NMA showed that there was no clinically significant difference between individual oral ASAs in terms of their effectiveness in inducing clinical remission. However, a dose effect observed. A second NMA was conducted (combined NMA) which pooled trials reporting low dose oral ASAs into one treatment group, and trials reporting high dose oral ASAs into another treatment group. The oral ASAs were grouped into low and high doses based on the recommended doses in the BNF[63] and corroborated by GDG opinion. The dose ranges are shown in Table 40.

The clinical outcome of the combined NMA was clinical remission as it was considered by the GDG to be an important measure of disease activity. In addition, the majority of relevant studies reported this outcome so the results could be aggregated. The results of the combined NMA informed the clinical inputs in this economic analysis.

Table 40: Oral ASA doses used in the combined network meta-analysis

Drug treatment	Lower dose of range stated in the BNF	Higher dose of the range stated in the BNF
Aminosalicylates	• Mesalazine (≥1.6-2.4g) • Sulphasalazine (4-6g) • Olsalazine (1-<1.5g)	• Mesalazine (>2.4g) • Sulphasalazine (>6g) • Balsalazide (≥ 6≤6.75g)[a] • Olsalazine (≥1.5g)

(a) The Balsalazide dose ranges from ≥ 6≤6.75g in order to include a study using a dose of 6.6g; this was considered to be likely to have a similar efficacy to 6.75g.

The following observations were made in the selection of drugs in the strategies:

- A low dose oral ASA therapy could be followed by a regimen containing a high dose oral ASA but not vice versa. The GDG considered this to be a logical step in the treatment pathway as a dose effect was observed in the clinical review.
- For first line treatment, the following drugs were compared - low dose oral ASA, high dose oral ASA, high dose ASA + beclometasone and high dose oral ASA + topical ASA. In the clinical review section, a dose effect was not observed for topical ASAs; therefore doses in the model are based on standard BNF doses. Prednisolone was not considered as a first line option based on GDG opinion that use of steroids would be delayed in clinical practice to avoid steroid associated side effects.
- The GDG elected to exclude monotherapy with topical preparations from the model for several reasons:
  - Limited studies were identified in the clinical review that trialled these drugs in a cohort that had predominantly left sided or extensive ulcerative colitis.
  - In these studies, the dose and preparation of the topical ASAs did not appear to affect clinical or endoscopic outcomes.
  - In addition, the GDG felt that using a topical treatment with limited local release would not be appropriate to treat extensive disease.
- The use of high dose oral ASA administered alone or in combination with either a topical ASA or beclometasone was considered in patients who failed first line treatment with low dose oral ASA.

The use of high dose oral ASA with either topical ASA or beclometasone was considered for those who failed first line treatment with high dose oral ASA.

- Patients who had failed ASA therapy altogether were switched to prednisolone. The GDG noted that in clinical practice patients, prednisolone could be added on to existing ASA therapy. However this could not be modelled due to lack of clinical data for the use of ASA and prednisolone in combination.
- The final stage in all strategies following prednisolone failure was admission to hospital as patients are assumed to have progressed to severe UC. The treatment sequence for severe disease was not explicitly modelled as this was beyond the scope of this question. Therefore the simplifying assumption was made that inpatients received intravenous drugs which would lead to remission in most patients. Those who failed to respond required surgery to induce remission.

The ten treatment strategies compared are summarised in Table 41.

Table 41: Treatment strategies in the model

Strategy	1st line	2nd line	3rd line	4th line	5th line
1	High dose oral ASA	high dose oral ASA + topical ASA	prednisolone	inpatient	
2	High dose oral ASA	prednisolone	inpatient		
3	Low dose oral ASA	prednisolone	inpatient		
4	Low dose oral ASA	high dose oral ASA + topical ASA	prednisolone	inpatient	
5	Low dose oral ASA	high dose oral ASA	prednisolone	inpatient	
6	Low dose oral ASA	high dose oral ASA	high dose oral + topical ASA	prednisolone	inpatient
7	High dose oral ASA + topical ASA	prednisolone	inpatient		
8	High dose oral ASA + oral beclometasone	prednisolone	inpatient		
9	Low dose oral ASA	high dose oral ASA + oral beclometasone	prednisolone	inpatient	
10	High dose oral ASA	high dose oral ASA + oral beclometasone	prednisolone	inpatient	

5.1.2.3 Population

The population entering the model were adults with active mild to moderate left sided or extensive UC. Author reported definitions of disease activity were used, in line with the clinical review protocol. Left sided or extensive disease was defined as inflammation greater than 30-40cm (see Appendix C). Patients failing to respond to prednisolone were assumed to have progressed to more severe disease. The treatment sequence for severe disease was not explicitly modelled as this was beyond the scope of this question.

5.1.2.4 Time horizon

The time horizon considered in the base case model was 28 weeks. This was set to reflect the longest treatment sequence in the model which consists of five lines of treatment. The trials included in the NMA had varying durations as shown in Table 42. Data from oral ASA trials showed that the rate of remission or withdrawals tapered off as treatment time increased enabling an inference to be made that the trial durations were sufficient to capture health effects. Therefore, an average of the trial durations was used in the model following GDG approval. The trials addressing combination

treatments were of shorter duration than ASA only trials. It was noted that the shorter duration may unfairly favour combination treatments in terms of cost impact and QALY gain. In order to consider this uncertainty, a sensitivity analysis was conducted were the treatment duration was set to 8 weeks for all drugs.

Although prednisolone efficacy was based on a single 3 week trial, the GDG elected to model it over an 8 week period. This was done to reflect clinical practice as prednisolone is usually tapered off according to a recognized reducing dose schedule. The durations for the other drugs were agreed by the GDG and are shown in Table 42.

Table 42: Drug treatment durations

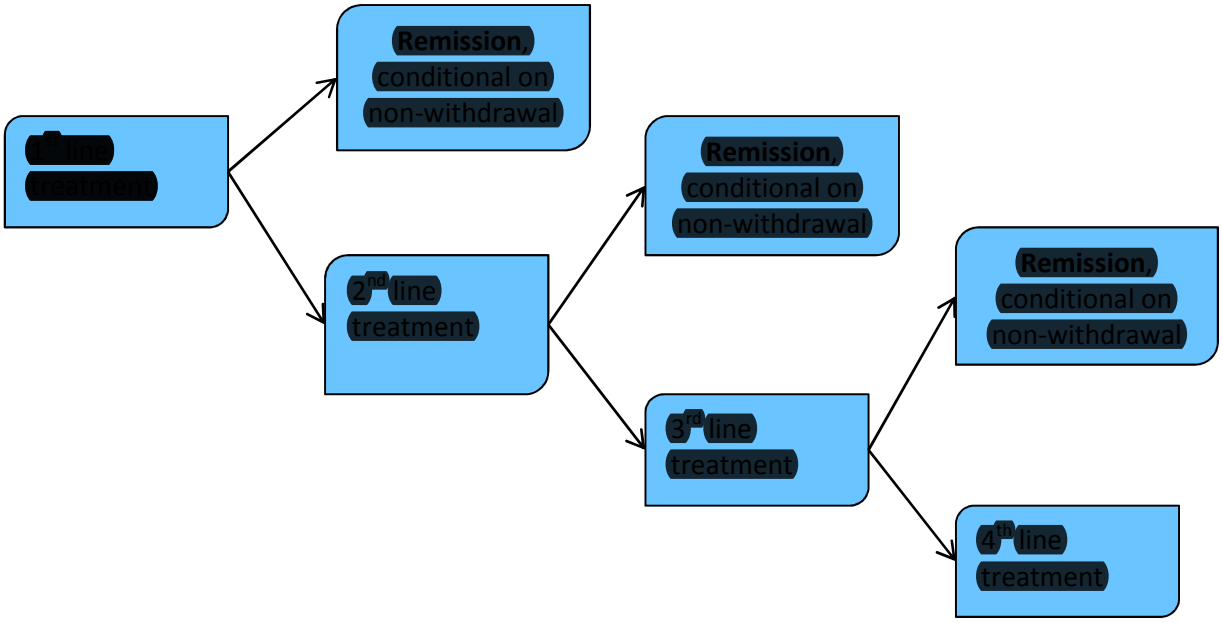
Drug	Treatment duration reported in trials	Treatment duration in model
Low dose oral ASA	6-12 weeks	8 weeks
High dose oral ASA	6-12 weeks	8 weeks
High dose oral ASA + topical ASA	4 weeks	4 weeks
High dose oral ASA + beclometasone	4 weeks	4 weeks
Prednisolone	3 weeks	8 weeks

5.1.2.5 Approach to modelling

5.1.2.5.1 Model structure

A decision tree was constructed in which the QALY gain is driven by the proportion of people in whom remission is successfully induced. Author reported definitions of remission were used in line with the clinical review. Remission was conditional on not having withdrawn from therapy due to adverse events. People who withdrew or failed to respond to therapy at the end of a course of treatment moved on to the next treatment in the sequence. The GDG were aware that specific adverse events could be attributed to certain drugs included in the model. They however concluded that the reporting of adverse events in the RCTs was not sufficient to model specific treatment related adverse events. Withdrawal from treatment was therefore used as a proxy for adverse events. This implies that the costs and dis-utilities pertaining to adverse events for each treatment would be captured by the cost of treating withdrawals and the associated utility loss from remaining in active disease. To capture the benefits of inducing remission early, patients in whom remission is induced on the first line of treatment will gain more QALYs than those who respond on subsequent lines of treatment. The structure of the model is shown in Figure 327.

Figure 327: Model structure



5.1.2.6 Uncertainty

5.1.2.6.1 Probabilistic analysis

The model was built probabilistically to take account of the uncertainty around parameter point estimates. In order to do this, probability distributions based on error estimates from data sources, for example the standard error around a point estimate, were defined for each model input. When the model was run, a value for each input was randomly selected from its respective probability distribution. This was done repeatedly – 1000 times and results were summarised. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using the methods as described by Koehler and colleagues[29]. It is set to ensure that the Monte Carlo error is not more than 5% of the standard error for these parameters. The types of distribution used in the model can be found in Table 43.

Table 43: Distributions used in the model

Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Cost and resource use	Gamma	Bounded at 0. Derived from mean and standard error	α = (mean/SEM)2 λ = mean/SEM2
Resource use	Triangular	Derived from expert opinion or reported in data source.	Min = minimum value Likeliest = mean Max = maximum value
Treatment effects, utility weights and reference costs	Lognormal	Bounded at 0. Derived from log (mean) and standard error.	μ = ln(RR) SD(μ) = (ln[UpperCI] – ln[lowerCI])/1.96*2

5.1.2.6.2 Uni- and multi-variate sensitivity analysis

Uni-variate (single variable) sensitivity analyses were conducted in order to test the robustness of model results to changes in key parameters. In one way sensitivity analysis, one parameter is varied while all other parameters are kept constant and the effects of changing this parameter on model results are explored. The analyses are described in Table 64. A multi-variate (multiple variable)

sensitivity analyses was also conducted where more than one parameter was varied while other parameters were kept constant. The analysis is described in Table 65.

5.1.2.7 Model inputs

5.1.2.7.1 Summary table of model inputs

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs were validated by the GDG. Summaries of the model inputs used in the base-case analysis are provided in Table 44, Table 45, Table 46 and Table 47. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 44: Summary of model inputs: clinical probabilities of withdrawal and remission conditional on non-withdrawal

Variable	Probability of withdrawal	Probability of remission conditional on non-withdrawal
Low dose oral ASA	6.6%	31.6%
High dose oral ASA	5.2%	40.3%
High dose oral ASA + topical ASA	6.4%	48.0%
High dose oral ASA + beclometasone	1.2%	64.2%
Prednisolone	0%[a]	52.9%

Source: clinical review and NMA
(a) Based on GDG consensus as no withdrawals data from trial

Table 45: Summary of model inputs: proportions of inpatients going into remission

Variable	Proportion of inpatients	Source
Intravenous drug-induced remission	91%	GDG
Surgical-induced remission	9%	GDG

Table 46: Summary of model inputs: utility weights

Variable	Estimate	Range	Reference
Remission	0.94	0.937-0.943	Poole et al[103]
Active disease	0.775	0.751-0.800	Poole et al[103]

Table 47: Summary of model inputs: costs

Variable	Cost	Source
Drugs		
Course of low dose oral ASA	£63.59	MIMS[1], Drug tariff[97]
Course of high dose oral ASA	£126.06	MIMS[1], Drug tariff[97]
Course of high dose oral ASA + topical	£167.57	MIMS[1], Drug tariff[97]

Variable	Cost	Source
ASA		
Course of high dose oral ASA + oral beclometasone	£115.82	MIMS[1], Drug tariff[97]
Course of prednisolone	£21.38	MIMS[1], Drug tariff[97]
Inpatient treatment		
Intravenous therapy	£2464.20	NHS reference costs[28] (code FZ37G, FZ37H, FZ37I, FZ37J)
Surgery	£7404.44	NHS reference costs[28] (code FZ08A, FZ08B)
Tests		
Full blood count	£3.00	NHS reference costs[28] (code DAP823)
Renal function test	£1.00	NHS reference costs[28] (code DAP841)
Consultations (per hour)		
Consultant Gastroenterologist	£137.00	PSSRU[23]
General practitioner	£127.00	PSSRU[23]
IBD nurse specialist	£53.00	PSSRU[23]
Telephone consultation with IBD nurse specialist	£23.00	Payments by results guidance 2009-10[29]
Specialist registrar	£59.00	PSSRU[23]
Non consultant post-surgical visit	£56.84	NHS reference costs[28] (code 301S)
Weekly consultation costs for patients with relapse	£7.75	Calculation
Weekly consultation costs for patients in remission	£1.38	Calculation

5.1.2.8 Baseline events (withdrawal and remission)

Baseline risks were pooled from the placebo arms of RCTS included in the clinical review by using the generic inverse variance method. This provided the baseline log odds of withdrawals due to adverse events and spontaneous remission conditional on non-withdrawal. The results are presented in Table 48.

Table 48: Baseline events

Treatment	Odds of withdrawal (log scale)	Odds of remission conditional on non-withdrawal (log scale)
No treatment (Placebo)	-2.406	-1.525

5.1.2.9 Relative treatment effects (withdrawal and remission)

Treatment-specific probabilities for withdrawal and remission conditional on non-withdrawal were obtained from the combined NMA conducted. A brief outline of the methods can be found below with the full methodology reported in Appendix I.

A conditional logistic regression NMA was conducted to take into account the negative correlation between withdrawals and remission. This is because it is assumed that people who withdraw cannot go into remission, and similarly people counted as being in remission have not withdrawn due to adverse events. In other words, the two events are mutually exclusive. Therefore, treatment effects for the model had to be accounted for such that the number of withdrawals and remissions could not exceed the number of people in the trial. This was captured by removing the number of withdrawals from the denominator when entering data for remission into WinBUGS. The calculation is described in Equation 1. The NMA produced estimates of treatment effects measured on the log odds scale. The results are shown in Table 49.

Equation 1: Calculating probability of remission conditional on non-withdrawal

$$P(R|W^c) = \frac{P(R)}{1 - P(W)}$$

Where:

$P(R|W^c)$ = probability of remission conditional on non-withdrawal

P(R) = probability of remission

P(W) = probability of withdrawal

Table 49: Estimates of treatment effects from NMA

Treatment	Odds of withdrawal (log scale)	Odds of remission conditional on non-withdrawal (log scale)
Low dose oral ASA	-0.239	0.754
High dose oral ASA	-0.498	1.132
High dose oral ASA + topical ASA	-0.283	1.447
High dose oral ASA + beclometasone	-1.979	2.108
Prednisolone	-	1.641

Withdrawals were assumed to occur at the end of a treatment cycle. People who withdrew due to adverse events while on any dose of oral ASA moved to the next non-ASA treatment in the sequence. The GDG noted that in reality, clinicians may elect to try another type of ASA before switching patients to other therapies. However, a simplifying assumption was made that patients who had an adverse reaction to one ASA might have an adverse reaction to all ASAs. Therefore in the model they were switched to a non-ASA therapy if they withdrew.

In the model, there were no withdrawals due to adverse events while on prednisolone treatment. This is because withdrawal data could not be obtained from the trial included in the NMA. The GDG considered that rarely would a side effect be observed that would necessitate withdrawal from treatment. In addition, due to disease severity at this stage, the primary aim would be to induce remission and delay use of intravenous therapy.

Relative treatment effects were calculated by adjusting the baseline log odds shown in Table 48 by the treatment specific log odds shown in Table 49. The symbols used to denote the variables in the calculation are described in Table 50.

Table 50: Explanation of symbols from equations

Symbol for equation	Explanation

Symbol for equation	Explanation
BO_w	Baseline odds for withdrawal
$BO_{r\|w^c}$	Baseline odds for remission conditional on non-withdrawal
θ_w	Treatment specific odds for withdrawal
$\theta_{r\|w^c}$	Treatment specific odds for remission conditional on non-withdrawal
OR_w	Treatment specific log odds ratio for withdrawal
$OR_{r\|w^c}$	Treatment specific log odds ratio for remission conditional on non-withdrawal
p_w	Probability of withdrawal
$p_{r\|w^c}$	Probability of remission conditional on non-withdrawal

The calculation is as follows:

$$\theta_w = Ln(OR_w) + Ln(BO_w)$$

$$\theta_{r|w^c} = Ln(OR_{r|w^c}) + Ln(BO_{r|w^c})$$

And:

$$p_w = \frac{e^{(\theta_w)}}{1 + e^{(\theta_w)}}$$

$$p_{r|w^c} = \frac{e^{(\theta_{r|w^c})}}{1 + e^{(\theta_{r|w^c})}}$$

The calculation enabled baseline and relative treatment effects to be modelled on the same log odds scale. The final treatment-specific probabilities used in the model can be seen in Table 51.

Table 51: Absolute probabilities in the model

	Probability of withdrawal				Probability of remission conditional on non-withdrawal			
Variable	mean	sd	median	CI	mean	sd	median	CI
Low dose oral ASA	6.6%	0.22	6.6%	4.4%, 9.8%	31.6%	0.14	31.5%	26.0%, 37.9%
High dose oral ASA	5.2%	0.24	5.2%	3.3%, 8.0%	40.3%	0.15	40.2%	33.3%, 47.9%
High dose oral ASA + topical ASA	6.4%	0.63	6.3%	2.0%, 19.2%	48.0%	0.42	47.9%	29.0%, 67.8%
High dose oral ASA + beclometasone	1.2%	1.46	1.4%	0.0%, 12.8%	64.2%	0.42	64.0%	44.4%, 80.6%
Prednisolone	-	-	-	-	52.9%	0.83	52.1%	19.5%, 86.2%

Combination treatment with high dose oral ASA +beclometasone was associated with the highest probability of remission conditional on non-withdrawal. Possible inconsistencies with the withdrawal data were noted. Firstly, withdrawal rates were higher for low dose oral ASA compared to high dose oral ASA. In additional withdrawal from high dose oral ASA + beclometasone was lower than the high

dose oral ASA + topical ASA or high dose oral ASA alone. The high dose oral ASA + beclometasone data was based on a single study however which could explain this inconsistency.

Inpatient treatment and surgery

Patients who failed to respond to prednisolone in each strategy were assumed to have progressed to more severe disease and were hospitalised. Based on clinical practice as described by the GDG, inpatients would typically start on a course of intravenous steroids and failing response to that would be administered intravenous ciclosporin. Infliximab could be administered in line with the NICE technological appraisal recommendation[93,95]. As this model however was concerned with the pathway for mild to moderate disease, the specific treatments for severe disease were not explicitly modelled. Therefore the simplifying assumption was made that inpatients received intravenous drugs which would lead to remission in most patients. Those who failed to respond required surgery to induce remission. The GDG provided estimates on the proportion of inpatients that would have drug-induced remission and surgically-induced remission. The estimates are shown in Table 52.

Table 52: Probabilities of inpatient remission

Variable	Proportion of inpatients
Intravenous drug-induced remission	91%
Surgical-induced remission	9%

5.1.2.10 Utilities

For economic evaluation, a specific measure of Health Related Quality of Life (HRQoL) known as utility is required to calculate Quality Adjusted Life Years (QALYs). Utilities indicate the preference for health states on a scale from 1 (perfect health) to negative infinity. Death in this model is considered to have a utility of 0. The NICE reference case[94] specifies that the preferred utility assessment tool is the EQ-5D instrument.

A systematic search identified studies with appropriate utility weights to use in the model. A description of the studies is shown in Table 53.

Table 53: Relevant utility data

Study	Description	Values
Poole[103]	Ulcerative colitis disease activity index (UCDAI) scores and EQ5D scores were collected from 126 patients enrolled in a trial comparing oral and topical mesalazine with oral mesalazine alone. 92% of patients have mild/moderate UC while 8% had severe UC. A model was developed to predict EQ5D scores based on individual abbreviated-UCDAI items. The algorithm was used to predict EQ5D scores for patients with differing UC severities enrolled in the Phase IV PODIUM (Pentasa once daily in ulcerative colitis for maintenance of remission) study.	Remission: 0.940 Mild/moderate disease: 0.775 Severe relapse: 0.660
Prenzler[108]	The health states modelled in this paper were assigned utilities based on disease severity. The utility data used in the paper was based on two studies. The utility scores were obtained via a time trade off approach and the EQ5D from a sample of 151 patients with	Remission: 0.845 Active UC: 0.589 Severe relapse: 0.317

Study	Description	Values
	UC.	
Yen[137]	The health states modelled were assigned utilities based on disease severity. The utilities were derived from various studies using the time trade off method. Some assumptions were made based on similarities with Crohn's disease.	Remission: 0.919 Outpatient flare: 0.770 Inpatient flare: 0.608

Utility weights estimated by Poole[103] were used in the base case analysis because the data was obtained from a UK population which had similarities with the cohort modelled in this analysis. In addition, EQ5D was estimated which is in line with the NICE reference case and utilities were based on clinical severity as defined by the UCDAI. UCDAI scores have been reviewed in the clinical review section of this guideline.

A sensitivity analysis was conducted to test the robustness of the model results and is described in Table 64.

5.1.2.11 Resource use and cost

Consultations

The GDG provided estimates on the number of consultations and the average length of consultation time that people with active UC would receive, regardless of the treatment they are taking. Unit costs were obtained from the PSSRU[23] and adjusted by the consultation time to estimate average weekly costs of consultations. The inputs are summarised in Table 54.

Table 54: Consultations for people with active disease

Type of consultation	Frequency (every 4 weeks)	Length of consultation (minutes)	Cost per hour[a]
Consultant gastroenterologist	10 visits per 100 patients	20	£137
General practitioner	40 visits per 100 patients	17.2[a]	£127.00
IBD nurse specialist	30 visits per 100 patients	20	£53.00[b]
Telephone consultation with IBD nurse specialist	20 calls per 100 patients	10	£23.00
Specialist registrar	10 visits per 100 patients	20	£59.00
Average weekly costs of consultation		£7.75	

(a) PSSRU[23]
(b) Payments by results guidance 2009-10[23]

The GDG also provided estimates of the nature and frequency of contacts that people in remission would have with the health service. The frequencies are shown in Table 55. It was assumed the length of consultations would be the same as for people with active disease but at a reduced frequency. In addition, it was also assumed that only 80% of patients would utilise these services.

Table 55: Frequency of consultations for people in remission

Type of consultation	Annual frequency
Consultant gastroenterologist	One per year (half of all people)
General practitioner	One per year (all people)
IBD nurse specialist	One per year (half of all people)
Telephone consultation with IBD nurse specialist	One per year (half of all people)
Specialist registrar	One per year (half of all people)

Based on these frequencies and cost data provided in the Table 54, an average weekly consultation cost of £1.38 was calculated for a person in remission.

Drugs

Mesalazines, such as Ipocol and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment on their relative efficacy. Therefore, for mesalazine preparations, only those addressed in the clinical review were used to inform drug costs in the model. The average costs of low dose and high dose oral ASAs were based on costs of the individual drugs and dose ranges described in Table 40 and the BNF[63]. Unit costs were obtained from the drug tariff[67] and MIMS[1]. Average costs of drugs were calculated if more than one preparation was identified from these sources. These costs are presented in Table 56, Table 57, Table 58, Table 59 and Table 60.

Table 56: Low dose oral ASA costs in the model

Cost item	Pack size	Cost per pack (£)	Daily dose (grams)
Pentasa SR Tab 500mg	100	30.74	2
Pentasa Gran Sach 1g M/R	50	30.74	2
Pentasa Gran Sach 2g M/R	60	73.78	2
Pentasa Tab 1g M/R	60	36.89	2
Mezavant XL Tab G/R 1.2g	60	62.44	2.4
Ipocol Tab E/C 400mg	120	41.62	2.4
Salofalk Tab G/R 500mg	100	32.38	1.5
Salofalk Gran Sach G/R 1.5g M/R	60	48.85	1.5
Salofalk Gran Sach G/R 1g M/R	50	28.74	2
Salofalk Gran Sach G/R 500mg M/R	100	28.74	1.5
Salofalk Tab E/C 250mg	100	16.19	1.5
Asacol MR Tab E/C 400mg	90	29.41	2.4
Asacol MR Tab E/C 800mg	180	117.62	2.4
Sulfasalazine Tab E/C 500mg	100	10.14	4
Sulazine EC Tab 500mg	112	14.83	4
Sulfasalazine Tab 500mg	112	7.83	4
Salazopyrin En_Tab 500mg	112	8.43	4
Salazopyrin Tab 500mg	112	6.97	4
Dipentum Tab 500mg	60	21.18	1
Dipentum Cap 250mg	112	19.77	1
Average cost per 8 week course		£63.59	

Source: *MIMS® and GDG*

Based on the costs and doses in Table 56, an average cost of £63.59 was calculated for an 8 week course of low dose oral ASA in the base case. The total cost including consultations was £125.59.

Table 57: High dose oral ASA costs in the model

Cost item	Pack size	Cost per pack (£)	Daily dose (grams)
Pentasa SR Tab 500mg	100	30.74	4
Pentasa Gran Sach 1g M/R	50	30.74	4
Pentasa Gran Sach 2g M/R	60	73.78	4
Pentasa Tab 1g M/R	60	36.89	4
Mezavant XL Tab G/R 1.2g	60	62.44	4.8
Mesalazine Tab E/C 400mg	120	41.62	4.8
Salofalk Tab G/R 500mg	100	32.38	3
Salofalk Gran Sach G/R 1.5g M/R	60	48.85	3
Salofalk Gran Sach G/R 1g M/R	50	28.74	4
Salofalk Gran Sach G/R 500mg M/R	100	28.74	3
Salofalk Tab E/C 250mg	100	16.19	3
Asacol MR Tab E/C 400mg	90	29.41	4.8
Asacol MR Tab E/C 800mg	180	117.62	4.8
Sulfasalazine Tab E/C 500mg	100	10.14	8
Sulazine EC Tab 500mg	112	14.83	8
Sulfasalazine Tab 500mg	112	7.83	8
Salazopyrin En_Tab 500mg	112	8.43	8
Salazopyrin Tab 500mg	112	6.97	8
Dipentum Tab 500mg	60	21.18	3
Dipentum Cap 250mg	112	19.77	3
Balsalazide 750mg	130	30.42	6.75
Average cost per 8 week course		£126.06	

Source: *MIMS® and GDG*

Based on the costs and doses in Table 57, an average cost of £126.06 was calculated for an 8 week course of high dose oral ASA in the base case. The total cost including consultations was £188.05.

Table 58: Topical ASA costs in the model

Cost item	Pack size	Cost per pack (£)	Daily dose (grams)
Asacol 1g foam enema	14	26.72	2
Pentasa 1g retention enema	7	17.73	1
Salofalk 2g liquid enema	7	29.92	2
Salofalk 1g rectal foam	14	30.17	2

Source: *MIMS® and GDG*

Based on the average costs of high dose oral ASA shown in Table 57, and the data in Table 58, an average cost of £167.57 was calculated for a 4 week combination therapy of high dose oral ASA + topical ASA in the base case. The total cost including consultations was £198.57.

Table 59: Beclometasone costs in the model

Drug	Pack size	Cost per pack (£)	Daily Dose (mg)
Beclometasone 5mg tablets	30	56.56	5

Source: *MIMS*[4]

Based on the average cost of high dose oral ASA shown in Table 57, and the data in Table 59, an average cost of £115.82 was calculated for a 4 week combination therapy of high dose oral ASA + beclometasone in the base case. The total cost including consultations was £146.82.

Table 60: Prednisolone costs in the model

Cost item	Pack size	Cost per pack(£)	Dose
Prednisolone 5 mg	28	0.96	40 mg initially then tapered by 5mg weekly
Prednisolone e/c 5 mg	28	3.79	
Average cost per 8 week course		£21.38	

Source: *MIMS*[4] *and GDG*

Based on the data in Table 60, an average cost of £21.38 was calculated for an 8 week course of prednisolone in the base case. The total cost including consultations was £83.37.

Drug-specific tests

Drug-specific tests were based on the recommendations in the BNF[63] and were verified by the GDG. People were assumed to have renal function and blood tests after being on an ASA for 3 months, then once annually. The frequency of tests over a strategy is therefore based on amount of time spent receiving oral ASA therapy. Consequently only patients in strategies 1,4,5,6,9 and 10 who completed oral ASA courses (regardless of treatment outcome) were assumed to have one renal and one blood test. The unit costs of tests are summarised in Table 61.

Table 61: Tests for people on oral ASAs

Tests	Cost per test	Source
Full blood count	£1	NHS reference costs[28] (code DAP823)
Renal function	£3	NHS reference costs[28] (code DAP841)

Cost of inpatient drug treatment

The cost of in-patient drug treatment was estimated from NHS reference costs[28]. As the reference costs are populated by taking into consideration all the care a patient would receive while admitted, drug costs have not been calculated separately. Average weighted costs were calculated based on procedures listed under the HRG codes shown in Table 62. The overall cost of inpatient drug treatment was assumed to be £2,464 in the model.

Table 62: Inpatient costs

Description	HRG	Weight	Cost
Inflammatory Bowel Disease with length of stay 2 days or more with Major CC with Interventions	FZ37G	8.1%	£3,566
Inflammatory Bowel Disease with length of stay 2 days or more with Major CC without Interventions	FZ37H	14.6%	£2,516
Inflammatory Bowel Disease with length of stay 2 days or more without Major CC with Interventions	FZ37I	34.2%	£2,318
Inflammatory Bowel Disease with length of stay 2 days or more without Major CC without Interventions	FZ37J	43.1%	£2,355

Description	HRG	Weight	Cost
Average inpatient costs		£2,464	

Source: *NHS reference costs*[28]

Cost of surgery

Average weighted costs were calculated based on surgical procedures such as total colectomy, panproctocolectomy and ileostomy. The procedures were identified in the NHS reference costs[28] under 2 HRG codes –FZ08A and FZ08B (Table 63) and were verified by the GDG. Patients who had surgery were assumed to have a post-operative consultation which was costed at £56.84 (Table 47). The overall cost of surgery was assumed to be £7,460 in the model.

Table 63: Surgery costs in model

Description	HRG	Weight	Cost
Complex Large Intestine Procedures with Major CC	FZ08A	31%	£9,606
Complex Large Intestine Procedures without Major CC	FZ08B	69%	£6,411
Average surgery cost		£7,460	

Source: *NHS reference costs*[28]

5.1.2.12 Computations

The mean cost and effectiveness of the competing strategies were calculated using Microsoft Office Excel 2007.

5.1.2.13 Calculating QALYs

In order to calculate the QALYs associated with a given treatment strategy, we consider both the probability of inducing remission for each individual treatment, and the time spent in remission over the course of the model. To do this, we partition the treatment strategy into individual treatments and calculate the number of weeks of remission and active disease that occur as a direct result of each treatment. These are then aggregated over the duration of the strategy and QALYs for a given strategy are calculated by multiplying the number of weeks of remission and active disease by the appropriate utility weights.

Figure 328: Calculating weeks of remission and active disease for a given treatment strategy

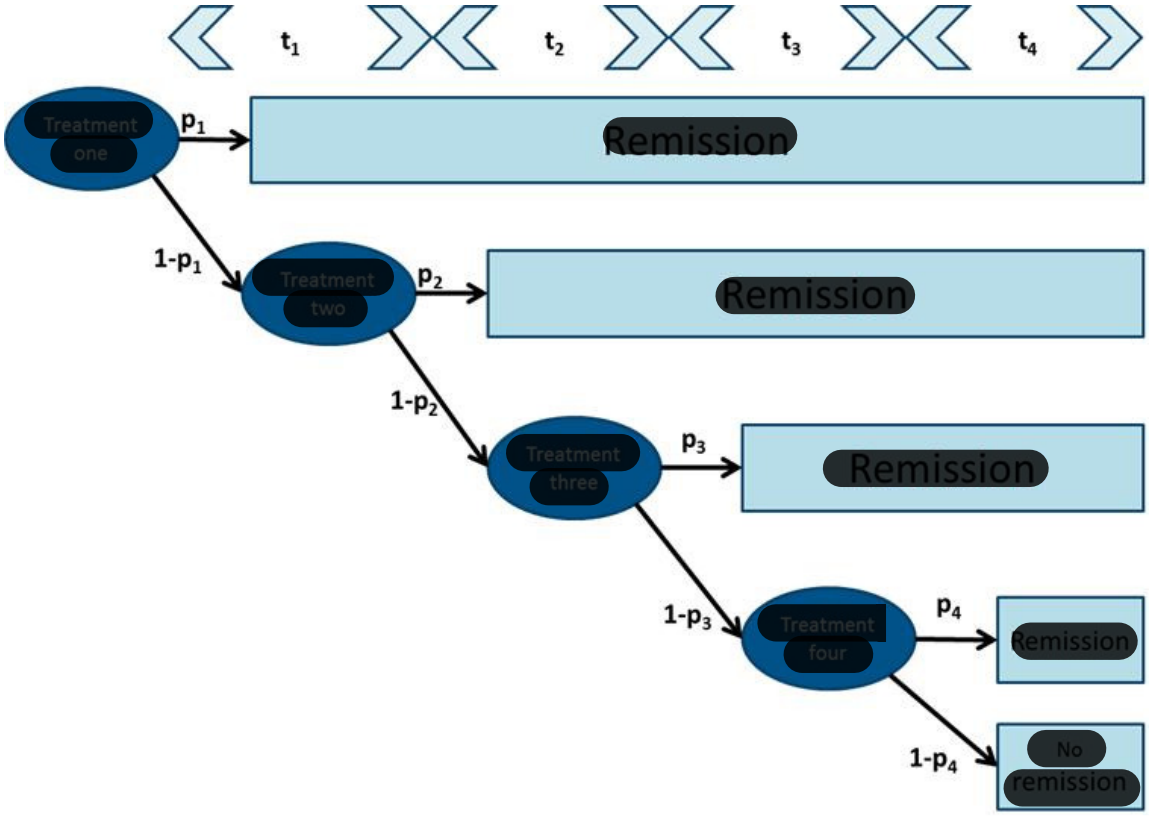


Figure 328 is a visual representation of how weeks of remission and active disease are calculated in the model. Note that, in the absence of data, it was assumed that for all people in whom remission is successfully induced, remission occurs half-way through treatment therefore the increase in utility is applied in the middle of a treatment cycle. People who go into remission remain there for the duration of the model.

It can be seen from the diagram that QALYs are calculated as follows:

Let p_1, p_2, p_3 and p_4 be the probabilities of successfully inducing remission with treatments 1, 2, 3 and 4 respectively.

Let t_1, t_2, t_3 and t_4 be the durations of treatment in weeks associated with treatments 1, 2, 3 and 4 respectively.

Let W_{R1}, W_{R2}, W_{R3} and W_{R4} denote the expected number of weeks of remission associated with treatments 1, 2, 3 and 4 respectively.

Let U_R and U_A be the utility weights associated with remission and active disease respectively.

Let H denote the time horizon in the model, which will be equal to the length of the longest treatment strategy and is 28 weeks in the base case.

Treatment one:

$$W_{R1} = p_1 \times \left(H - \frac{1}{2}t_1\right)$$

Treatment two:

$$W_{R2} = (1 - p_1) \times p_2 \times \left(H - t_1 - \frac{1}{2}t_2\right)$$

Treatment three:

$$W_{R3} = (1 - p_1) \times (1 - p_2) \times p_3 \times \left(H - t_1 - t_2 - \frac{1}{2} t_3\right)$$

Treatment four:

$$W_{R4} = (1 - p_1) \times (1 - p_2) \times (1 - p_3) \times p_4 \times \left(H - t_1 - t_2 - t_3 - \frac{1}{2} t_4\right)$$

Note that the term $p_4 \times (H - t_1 - t_2 - t_3 - t_4)$ is added to the equation for cases when the overall length of the treatment strategy is less than the time horizon. In the event that the duration of the treatment strategy is equal to the time horizon this term is equal to zero, since $H = t_1 + t_2 + t_3 + t_4$.

Then the total number of weeks of remission, $\boldsymbol{W_R}$ and number of weeks of active disease $\boldsymbol{W_A}$ are given by:

$$W_R = W_{R1} + W_{R2} + W_{R3} + W_{R4}$$

$$W_A = \boldsymbol{H} - W_R$$

And the total treatment specific QALYs, Q, are calculated as:

$$Q = \frac{1}{52} \times (W_R \times U_R + W_A \times U_A)$$

5.1.2.14 Probabilistic analysis in the model

In the probabilistic analysis, distributions were assigned to treatment effects, utilities and where possible, costs as described in Table 43. This was done to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.

Treatment effects:

To capture the uncertainty in treatment effects, a sample of 1000 random sets of treatment effects was taken from the NMA using the CODA function in WinBUGS. This has the advantage of preserving the correlation between variables, which would not be accounted for if they were sampled from their individual distributions. For the probabilistic analysis, in each simulation, a random set of treatment effects was chosen from the sample using random number generation.

Reference costs:

Costs of tests, in-patient treatment and surgery were obtained from NHS reference costs.in order to assign a distribution to reference costs, it was assumed that they followed a lognormal distribution and used the inter-quartile range to calculate an approximate standard error on the log scale.

Let $\boldsymbol{X}$ be the cost we seek to assign a distribution to, i.e. $\ln(\boldsymbol{X}) \sim \boldsymbol{Normal}(\boldsymbol{\mu}, \boldsymbol{\sigma^2})$

Let M be the mean associated with the cost.

Let $\boldsymbol{IQR}$ be the inter-quartile range associated with the cost.

Note that for normally distributed data:

$$IQR \approx 1.35\sigma$$

And noting that the standard error s, is related to the standard deviation by:

$$s = \frac{\sigma}{\sqrt{n}}$$

Then the standard error on the log scale can be calculated as:

$$\sigma = \frac{\ln(IQR)}{1.35 \times \sqrt{n}}$$

And therefore random draws from the distribution can be taken:

$$\ln(X) \sim Normal\left(ln\left(\mu - \frac{\sigma^2}{2}\right), \left(\frac{\ln(IQR)}{1.35 \times \sqrt{n}}\right)^2\right)$$

Utilities:

Utilities were sampled probabilistically by assigning lognormal distributions to utility decrements as described in (ref Briggs). Normal distribution parameters were converted to lognormal parameters by method of moments, as defined below:

Let $E[X]$ and $Var[X]$ be the mean and variance respectively, of the utility decrement U

Then the parameters of the lognormal distribution, μ and σ^2 are found by:

$$\mu = \ln(E[X]) - \frac{\ln\left(1 + \frac{Var[X]}{E[X]^2}\right)}{2}$$

$$\sigma^2 = \ln\left(1 + \frac{Var[X]}{E[X]^2}\right)$$

5.1.2.15 Calculating cost-effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in terms of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (e.g. £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NMB is used to identify the optimal strategy in the probabilistic-analysis simulations.

Let C_t and Q_t denote the mean costs and mean QALYs respectively, associated with a given treatment. Then the mean net monetary benefit, NMB_t is calculated as:

$$NMB_t = (£20{,}000 \times Q_t) - C_t$$

Where £20,000 per QALY represents the cost-effectiveness threshold in the NICE reference case.

This net benefit is calculated for each of the 1000 simulations in the probabilistic analysis. This means that the probability that a given treatment would be optimal can be estimated based on the number of times it has the highest net monetary benefit.

However, the strategy that is optimal overall is the one that has the highest net monetary benefit calculated using the mean costs and QALYs, where means were the average of the 1,000 simulated estimates.

5.1.2.16 Sensitivity analyses

The sensitivity of the results to changes to inputs and assumptions was tested by conducting seven uni-variate analyses as described in Table 64. SA1, SA2, SA3 and SA4 were conducted deterministically while SA5, SA6 and SA7 were conducted probabilistically.

Table 64: Uni-variate sensitivity analyses in the model

Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
SA1: Utility weights	The sensitivity of results to utility weights was tested by using estimates of utility from Prenzler[108]. This paper had the lowest values for utility data out of relevant studies identified. It was not used in the base case as the data was based on 2 abstracts.	Remission = 0.94 Active disease = 0.775	Remission = 0.845 Active disease = 0.589
SA2: Trial durations	In the base case, the combination treatments had durations of 4 weeks. This SA was conducted assuming these drugs were administered for 8 weeks to capture the effect of increased treatment costs.	• High dose oral ASA + beclometasone given for 4 weeks. • High dose oral ASA + topical ASA given for 4 weeks.	• High dose oral ASA + beclometasone given for 8 weeks. • High dose oral ASA + topical ASA given for 8 weeks.
SA3: GP contacts	It was decided to vary the frequency of visits to a GP due to a view that more patients may be treated in the community.	40 visits per 100 patients every 4 weeks	60 visits per 100 patients every 4 weeks
SA4: Prednisolone withdrawal	The withdrawal rate from prednisolone was set as zero in the base case by the GDG due to lack of data. This rate was varied to test impact on the results of the model.	Prednisolone withdrawal = 0%	Prednisolone withdrawal = 5%
SA5: Efficacy of non-1st line treatments	In the model, the efficacy data for 2nd and 3rd line treatments was from studies that trialled them as 1st line treatments. In this SA, the efficacy of these drugs was reduced when used as 2nd or 3rd line treatments. This was to reflect the fact that these treatments may not be as efficacious in this context.	As described in Table 44	Assumed that drugs were 30% less efficacious when used as non-1st line treatments.
SA6: Low withdrawal rates for oral ASAs	The withdrawal rates used in the model were obtained from the NMA. In order to assess if ASAs are better tolerated than the base case analysis suggests, lower withdrawal rates were used in	• Low dose ASA withdrawal = 6.6% • High dose ASA withdrawal = 5.2%	• Low dose ASA withdrawal = 6.4% • High dose ASA withdrawal = 4.4%

Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
	this SA. This data was obtained by reviewing the estimates of withdrawal for individual ASA preparations included in the NMA and using the lowest estimate available.		
SA7: High withdrawal rates for oral ASAs	The withdrawal rates used in the model were obtained from the NMA. In order to assess if ASAs are more poorly tolerated than the base case analysis suggests, higher withdrawal rates were used in this SA. This data was obtained by reviewing the estimates of withdrawal for individual ASA preparations included in the NMA and using the highest estimate available.	• Low dose ASA withdrawal = 6.6% • High dose ASA withdrawal = 5.2%	• Low dose ASA withdrawal = 33.1% • High dose ASA withdrawal = 5.4%

One multi-variate sensitivity analysis was conducted deterministically to address the effects of ASA costs on the model results. The analysis is described in Table 65.

Table 65: Multi-variate sensitivity analysis in the model

Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
Drug costs	In the base case, the daily costs of oral ASAs were based on an average of individual ASA preparations. The GDG was aware of the costs differences between different ASA preparations. This SA was conducted to capture the effect of ASA drug costs on the model results.	• Daily cost of low dose oral ASA = £1.14 • Daily cost of high dose oral ASA = £2.33	The daily costs of ASAs were varied from in £0.50 increments.

5.1.2.17 Model validation

The model was developed in consultation with the GDG. The model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of the model formulae and calculations. The model parameters and results were also assessed against the content of this appendix.

5.1.2.18 Interpreting results

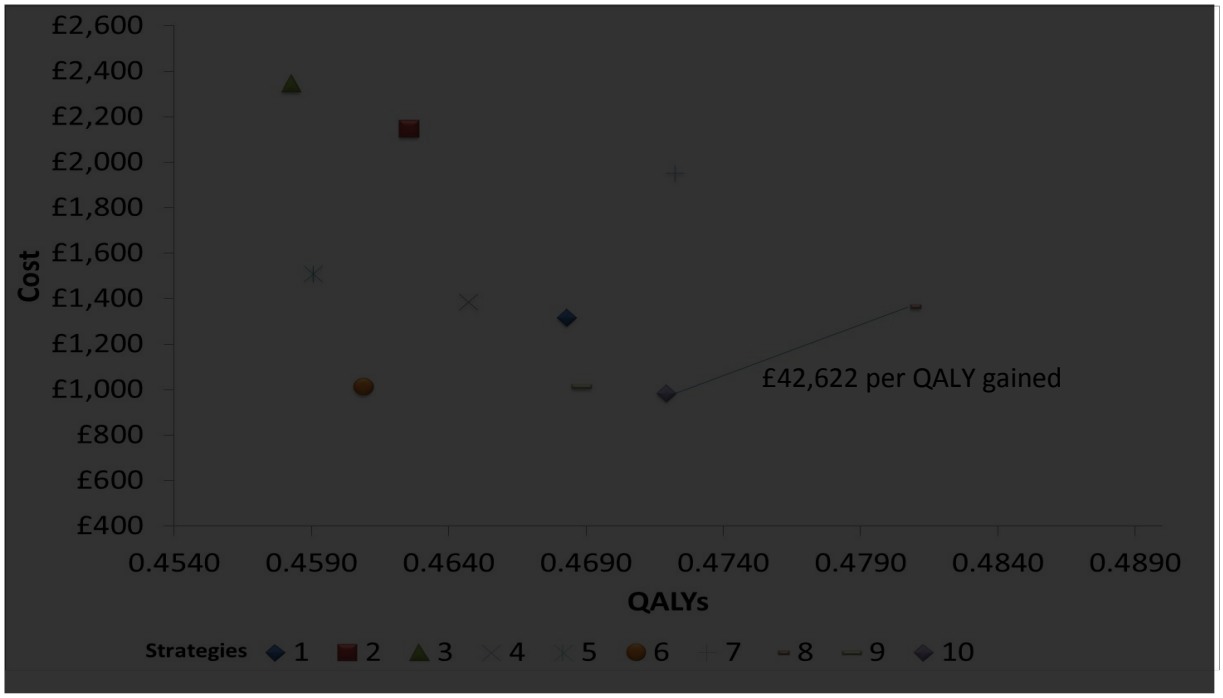
The strategy with the highest mean net monetary benefit is the one that should be recommended,[35] though the uncertainty around costs and QALYs should also be taken into consideration. Due to lack of data we were unable to explicitly capture the disutility of treatment-specific adverse events. This should be taken into consideration when interpreting the results.

5.1.3 Results

5.1.3.1 Base case results

In the base case, model inputs were set as shown in section 5.1.2.7 and the model was run probabilistically. Figure 329 shows the cost-effectiveness plane, depicting the mean costs and QALYs associated with each treatment strategy. Although strategy 8 yields better outcomes than strategy 10, it is more expensive. The QALY gained by moving from strategy 10 to strategy 8 does not justify the increased costs as an incremental cost-effectiveness ratio of £42,622 was calculated. This is significantly greater than the £20,000 per QALY cost-effectiveness threshold defined by NICE. Therefore the cost effective option is strategy 10. The strategy comprises of first line treatment with a high dose oral ASA with therapy escalated in the following sequence in the event of treatment failure; high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery.

Figure 329: Cost-effectiveness plane (mean costs and QALYs from probabilistic analysis)



Cost-effectiveness in the base case (per patient)

The probabilistic results allowed a ranking of the net monetary benefit to be developed and also showed the probability of an intervention being cost effective out of 1000 simulations. The cumulative ICERs for the 1000 simulations were plotted to check the stability of the ICERs. The ICERs were stable after approximately 200 simulations. Table 66 shows the breakdown of results. Strategy 10 had the highest NMB and was cost-effective in 54% of the simulations. This shows that although strategy 10 is likely to be cost effective, there is uncertainty in the results. This was highlighted by the confidence intervals around the ranking of the net monetary benefit which ranged from 1 to 4.

Table 66: Cost-effectiveness in the base case (per patient)

Strategy	Treatment sequence	Costs	QALYs	Cost per QALY gained (non-dominated)	NMB[a]	NMB rank (95% confidence interval)[a]	Probability of being most cost-effective strategy
10	High dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£984	0.472	£42,622 versus strategy 8	£8,454	1 (1,4)	54%
9	Low dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£1,012	0.469	Dominated	£8,364	2 (1,6)	5%
8	High dose oral ASA + beclometasone, prednisolone	£1,364	0.481	Dominated	£8,253	3 (1,7)	26%
6	Low dose oral ASA, high dose oral ASA, high dose oral ASA + topical ASA,	£1,013	0.461	Dominated	£8,205	4 (1,6)	12%

Strategy	Treatment sequence	Costs	QALYs	Cost per QALY gained (non-dominated)	NMB[a]	NMB rank (95% confidence interval)[a]	Probability of being most cost-effective strategy
	prednisolone						
1	High dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£1,316	0.468	Dominated	£8,050	5 (1,6)	3%
4	Low dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£1,386	0.465	Dominated	£7,908	6 (3,7)	0%
5	Low dose oral ASA, High dose oral ASA, prednisolone	£1,509	0.459	Dominated	£7,673	7 (5,9)	0%
7	High dose oral ASA + topical ASA, prednisolone	£1,953	0.472	Dominated	£7,492	8 (3,9)	0%
2	High dose oral ASA, prednisolone	£2,144	0.463	Dominated	£7,107	9 (8,9)	0%
3	Low dose oral ASA, prednisolone	£2,345	0.458	Dominated	£6,820	10 (9,10)	0%

(a) Using a willingness to pay threshold of £20,000 per QALY

In order to better understand the above results, a further break down can be found below.

Costs

Table 67 shows the total costs attributed to each strategy in the model. The total costs are calculated based on costs of drugs, tests, consultations, inpatient treatment and surgery. The cheapest treatment sequence is strategy 10 at a cost of £984. The strategy comprises of first line treatment with a high dose oral ASA with therapy escalated in the following sequence in the event of treatment failure; high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery.

Table 67: Mean costs in the base case (per patient)

Strategy	Treatments	Drug	Tests	Consultations (active)	Inpatient + surgery	Consultations (remission)	Total costs
1	High dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£713	£2	£102	£477	£22	£1,316
2	High dose oral ASA, prednisolone	£1,085	£0	£100	£939	£20	£2,144
3	Low dose oral ASA, prednisolone	£1,152	£0	£105	£1,070	£18	£2,345
4	Low dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£720	£2	£107	£536	£20	£1,386

Strategy	Treatments	Drug	Tests	Consultations (active)	Inpatient + surgery	Consultations (remission)	Total costs
5	Low dose oral ASA, high dose oral ASA, prednisolone	£760	£2	£130	£599	£18	£1,509
6	Low dose oral ASA , high dose oral ASA, high dose oral ASA + topical ASA , prednisolone	£540	£2	£130	£322	£19	£1,013
7	High dose oral ASA + topical ASA, prednisolone	£1,023	£0	£65	£841	£24	£1,953
8	High dose oral ASA + beclometasone, prednisolone	£705	£0	£54	£577	£27	£1,364
9	Low dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£518	£2	£101	£369	£22	£1,012
10	High dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£534	£2	£96	£328	£24	£984

Outcomes

Table 68 shows the amount of time spent in remission and active disease for each strategy. This information was used to calculate the total QALYs for each strategy as described in section 5.1.2.13. Strategy 8 was the most effective option as it yielded 20.05 weeks of remission and 7.95 weeks in active disease. This resulted in 0.481 QALYs. This is because the first treatment in the strategy which is high dose oral ASA + beclometasone is the most effective first line treatment enabling more patients to go into remission earlier.

Table 68: Mean clinical outcomes in the base case (per patient)

Strategy	Treatments	Weeks of remission	Weeks of non remission	QALYs
1	High dose oral ASA, high dose oral ASA + topical ASA, prednisolone	16.09	11.91	0.468
2	High dose oral ASA, prednisolone	14.28	13.72	0.463
3	Low dose oral ASA, prednisolone	12.92	15.08	0.458
4	Low dose oral ASA, high dose oral ASA + topical ASA, prednisolone	14.97	13.03	0.465
5	Low dose oral ASA, high dose oral ASA, prednisolone	13.18	14.82	0.459
6	Low dose oral ASA , high dose oral ASA, high dose oral ASA + topical	13.76	14.24	0.461

Strategy	Treatments	Weeks of remission	Weeks of non remission	QALYs
	ASA , prednisolone			
7	High dose oral ASA + topical ASA, prednisolone	17.34	10.66	0.472
8	High dose oral ASA + beclometasone, prednisolone	20.05	7.95	0.481
9	Low dose oral ASA, high dose oral ASA + beclometasone, prednisolone	16.26	11.74	0.469
10	High dose oral ASA, high dose oral ASA + beclometasone, prednisolone	17.23	10.77	0.472

Strategy 10 is the cheapest option but it is not the most effective. However, it comes out as cost effective when compared with strategy 8 (the most effective option). This is because the additional gain of 0.009 QALYs is not worth the additional £380 that would have to be spent to achieve that gain. This gives a cost per additional QALY gained of £42,622 which is well above the NICE £20,000 threshold.

5.1.3.2 Sensitivity analyses

5.1.3.2.1 Uni-variate sensitivity analysis

One-way sensitivity analyses as described in Table 64 were conducted in order to test the robustness of model results. SA1 – SA2 were conducted deterministically, while SA3 - SA7 were conducted probabilistically and the results are presented in Table 69. Strategy 10 (high dose oral ASA followed by high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery) was the most cost effective strategy (highest NMB) across all the analyses with the exception of SA5. As strategy 8 had only two lines of treatment (one of which was the most effective treatment choice), reducing the efficacy of non-1st line treatments had less of an effect on the NMB. Hence in SA5, it was the most cost effective strategy.

Table 69: One-way sensitivity analysis results –mean net monetary benefit per patient

Strategy	Treatments	Base case	SA1	SA2	SA3	SA4	SA5	SA6	SA7
1	High oral ASA , High oral ASA + topical ASA, Prednisolone	£8,050	£6,654	£9,303	£8,044	£7,993	£6,123	£8,041	£8,071
2	High oral ASA , Prednisolone	£7,107	£5,671	£8,538	£7,131	£7,013	£5,496	£7,122	£7,147
3	Low oral ASA, Prednisolone	£6,820	£5,344	£8,248	£6,848	£6,719	£4,983	£6,824	£6,533
4	Low oral ASA, High oral ASA + topical ASA, Prednisolone	£7,908	£6,475	£9,134	£7,902	£7,848	£5,730	£7,903	£8,141

Strategy	Treatments	Base case	SA1	SA2	SA3	SA4	SA5	SA6	SA7
5	Low oral ASA , High oral ASA, Prednisolone	£7,673	£6,172	£9,099	£7,676	£7,614	£5,626	£7,678	£7,970
6	Low oral ASA, High oral ASA, High oral ASA + topical ASA, Prednisolone	£8,205	£6,803	£9,610	£8,201	£8,188	£6,126	£8,204	£8,354
7	High oral ASA + topical ASA, Prednisolone	£7,492	£6,171	£8,609	£7,502	£7,397	£5,996	£7,487	£7,533
8	High oral ASA + oral Beclometasone, Prednisolone	£8,253	£7,057	£9,470	£8,271	£8,203	£7,231	£8,252	£8,270
9	Low oral ASA, High oral ASA + oral Beclometasone, Prednisolone	£8,364	£6,998	£9,656	£8,365	£8,333	£5,975	£8,364	£8,458
10	High oral ASA, High oral ASA + oral Beclometasone, Prednisolone	£8,454	£7,117	£9,766	[redacted]	£8,422	£6,339	£8,453	£8,463

**Using a willingness to pay threshold of £20,000 per QALY.*

5.1.3.2.2 Multi-variate sensitivity analysis

One multi-variate deterministic analysis as described in Table 65 was conducted to assess the effect of daily costs of oral ASA on the model results. Figure 330 shows the change to the NMB for each strategy as daily costs of ASAs are decreased or increased in £0.50 increments. The NMB decreased across all strategies, as the daily costs of ASAs increased. However, strategy 10 remained the cost effective strategy irrespective of the daily cost of ASA.

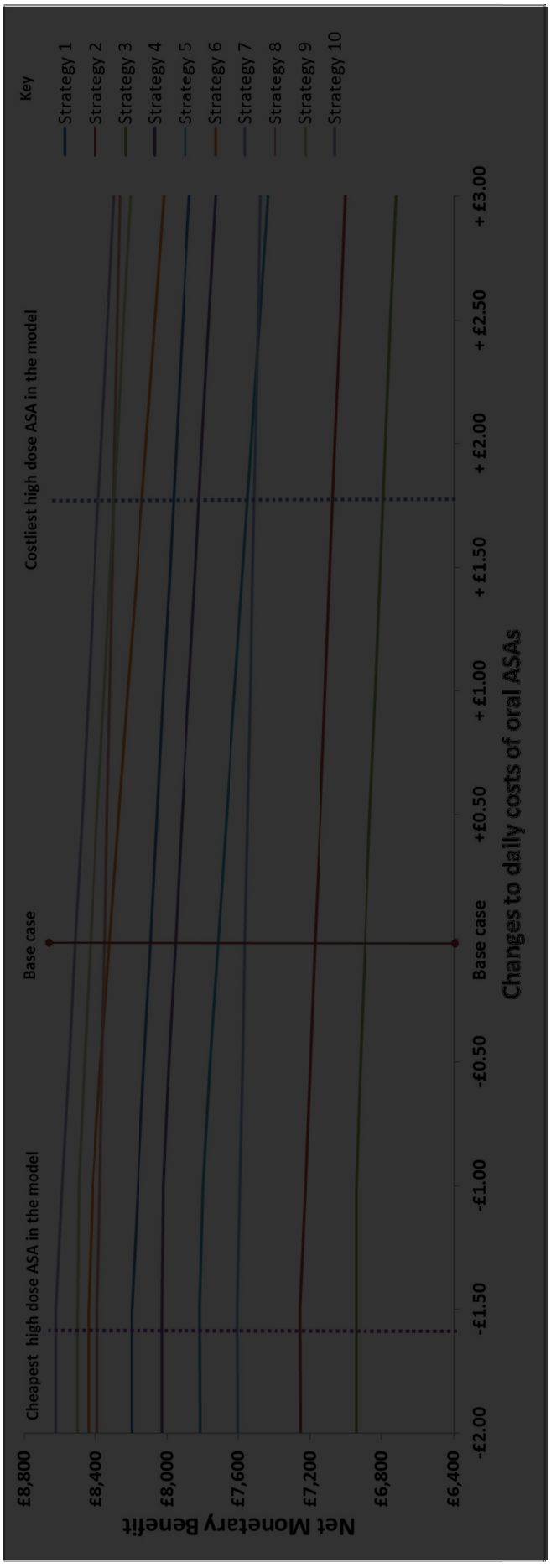


Figure 330: Effect of daily costs of oral ASAs on net monetary benefit

5.1.4 Discussion

5.1.4.1 Summary of results

The cost-effectiveness analysis shows that the most cost effective treatment strategy to induce remission in patients with mild to moderate left sided and extensive disease is high dose oral ASA followed by high dose oral ASA + beclometasone followed by prednisolone. This analysis was based on a conditional logistic regression network meta-analysis conducted using RCT data, acquisition costs, PSSRU costs and NHS reference costs. The results were robust to sensitivity analysis conducted.

5.1.4.2 Limitations & interpretation

The model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. Limitations of the model which impact on the interpretation of the results are as follows:

- Oral ASAs have been grouped into low and high doses. It is plausible that particular brands of ASAs may be slightly more or less efficacious than others but the differences were not considered to be clinically significant based on the NMA results. This uncertainty could mean that the effectiveness of ASAs may be under or over-estimated however the magnitude is unknown.
- Mesalazines, such as Ipocol and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment about the relative efficacy of these mesalazines hence caution should be exercised when generalising the results of this model.
- Patients who had failed ASA therapy altogether were switched to prednisolone. The GDG noted that in clinical practice patients, prednisolone could be added on to existing ASA therapy. However this could not be modelled due to lack of clinical data for the use of ASA and prednisolone in combination.
- The costs and dis-utilities of drug-specific adverse events were not explicitly modelled due to lack of robust data; however withdrawal from treatment was used as a proxy for adverse events. This means that the cost-effectiveness of all treatments strategies may have been over-estimated although the magnitude is unknown as each drug is likely to have a specific side-effect profile. The overestimation of the ICER would be greater for treatments that have more serious side effects compared to those with less serious side effects. This introduces uncertainty around interpretation of the results.
- The clinical data informing non-first line treatments were obtained from studies that had trialled the drugs as first line. This means that the effectiveness of certain treatments may have been over-estimated when used as a non-first line treatment options. Consequently, this would impact on the cost-effectiveness of the overall strategy. A sensitivity analysis was conducted to address this issue. All the treatment strategies compared became less cost effective however the most cost effective option was strategy 8 which comprises of first line combination treatment with a high dose oral ASA and oral beclometasone and switching to prednisolone in the event of treatment failure.

5.1.4.3 Generalisability to other populations / settings

The analysis was based on data obtained from an adult population hence may not be generalizable to paediatric populations. This is especially important as the dose ranges of ASAs were based on adult doses. A model relevant to the paediatric population could not be constructed due to paucity of clinical data.

The model applies to patients with mild to moderate left sided or extensive disease. Other extents of UC such as proctitis have not been addressed and as such treatment options used in the model may not be applicable. Similarly, in terms of disease activity, treatment of severe UC has not been explicitly modelled. There may be other treatment options for this population not captured in the model.

5.1.4.4 Comparisons with published studies

The results of relevant economic studies addressing this topic area have been summarised briefly in Table 39.

In the model, oral ASAs were addressed as a class based on the clinical review findings that there was no clinically significant difference between the individual ASA preparations. Hence, the model results cannot be compared to the Brereton[10] and Mackowiak[86] studies.

The study by Buckland[11] found a higher dose of ASA to be cost effective compared to a lower dose. This is supported by the model result. All strategies where the only difference was the use of either a low dose ASA or a high dose ASA first line that is, strategies 1 versus 4, 2 versus 3 and 10 versus 9, high dose ASA was always cost effective.

The study by Connolly[19] found combination treatment of oral and topical mesalazine was found to be more cost effective than oral mesalazine. This is supported by the model results as strategy 7 (high dose oral ASA + topical ASA followed by prednisolone) has a higher NMB than strategy 2(high dose oral ASA followed by prednisolone).

5.1.4.5 Conclusion and evidence statement

The original economic analysis suggests that high dose oral ASA followed by high dose oral ASA + beclometasone followed by prednisolone is the most cost effective treatment strategy to induce remission in patients with mild to moderate left sided or extensive ulcerative colitis.

5.2 Maintenance of remission

5.2.1 Introduction

This economic analysis explores the cost-effectiveness of different doses of aminosalicylates (ASAs) for the maintenance of remission in patients who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive ulcerative colitis (UC). This analysis incorporated results of the induction model described above therefore it does not address patients with proctitis and proctosigmoiditis. In addition the GDG identified that the treatment options for patients with proctitis and proctosigmoiditis was deemed to be less variable and hence modelling for this subgroup was not identified as high priority.

A study by Yen[137] assessed the cost-effectiveness of no maintenance therapy versus 5-ASA maintenance therapy in patients with mild to moderate UC. 5-ASA therapy was shown to increase the discounted QALYs per person yielding an incremental cost-effectiveness ratio (ICER) of £146,000/QALY. This figure was highly dependent on the daily cost of ASAs as a sensitivity analysis showed that the ICER was £10,306/QALY when cheaper drug costs of sulfasalazine were used. The GDG noted that there were issues surrounding the applicability of this study as some health state utilities were inferred from a Crohn's disease and the model was based on a non-UK population. The full study details can be found in Appendix G.

The network meta-analysis (described in Appendix I) conducted on oral ASA maintenance treatments provided effectiveness data for low dose oral ASAs and high dose oral ASAs. The GDG felt that

majority of patients would be on maintenance therapy after successful induction of remission and therefore considered this topic to be a top priority for original economic analysis. Hence, the original economic model presented here sought to address the question about the cost-effectiveness of different doses of ASAs for maintaining remission in people with ulcerative colitis.

5.2.2 Methods

5.2.2.1 Model overview

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective (PSS). Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[96].

5.2.2.1.1 Comparators

Two network meta-analyses (NMAs) were conducted addressing the use of oral ASAs for maintenance of remission in people who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive UC (Appendix I). A baseline NMA was conducted which addressed two outcomes; rate of relapse and withdrawals from treatment. The NMA didn't demonstrate any clinically significant differences between the lower doses of oral ASAs in terms of their effectiveness in maintaining remission. This was the same for the higher doses of oral ASAs. In the NMA, a dose effect was not observed between lower and higher doses of oral ASAs but in the clinical review a dose relationship was suggested. It was thought that the same groupings should be used as in the induction NMAs due to small event rates. It was also felt that because there was large uncertainty in the results, grouping the oral ASAs into low and high doses could strengthen the power to demonstrate an effect.

A second NMA (combined NMA) was therefore conducted which combined trials reporting low dose oral ASAs into one treatment group, and trials reporting high dose oral ASAs into another treatment group. The grouping was based on doses identified in the clinical review, recommended doses in the BNF[63] and GDG opinion. The dose ranges are shown in Table 70. The results of this NMA informed the clinical inputs in this economic analysis.

Table 70: Oral ASA doses used in the combined network meta-analysis

Drug treatment	Low maintenance dose oral ASA	High maintenance dose oral ASA
Aminosalicylates	Mesalazine (≤1.5g) [(a)] Salofalk (≤1.5g) Pentasa (≤2g) Asacol (≤1.2g) Olsalazine (≤1g) Balsalazide (≤3g) Sulfasalazine (≤2g)	Mesalazine (>1.5g) [(a)] Salofalk (>1.5g) Pentasa (>2g) Asacol (>1.2g) Olsalazine (>1g) Balsalazide (>3g) Sulfasalazine (>2g)

(a) For trials that do not specify the brand of mesalazine

The six comparators examined in the model were chosen by the GDG. The comparators explored the use of different doses of aminosalicylates (ASA) and are as follows:

- **No maintenance, returning to no maintenance strategy:** starting patients on no maintenance and returning to no maintenance after treating an outpatient flare.
- **No maintenance, returning to low dose ASA strategy:** starting patients on no maintenance and moving to a low maintenance dose ASA after treating an outpatient flare.
- **No maintenance, returning to high dose ASA strategy:** starting patients on no maintenance and moving to a high maintenance dose ASA after treating an outpatient flare.

- **Low dose ASA, returning to low dose ASA strategy:** starting patients on low maintenance dose ASA and returning to a low maintenance dose ASA after treating an outpatient flare.
- **Low dose ASA, returning to high dose ASA strategy:** starting patients on low maintenance dose ASA and moving to a high maintenance dose ASA after treating an outpatient flare.
- **High dose ASA, returning to high dose ASA strategy:** starting patients on high maintenance dose ASA and returning to a high maintenance dose ASA after treating an outpatient flare.

5.2.2.1.2 Population

The population entering the model are adults in remission who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive ulcerative colitis. Author reported definitions of disease activity were used, in line with the clinical review protocol. Left sided or extensive disease was defined as inflammation greater than 30-40cm (see Appendix C). The cohort starting age was chosen as 18 years as the GDG felt this represented a typical age of onset. The risk of mortality was assumed to be the same as that of the general UK population.

5.2.2.1.3 Time horizon

The time horizon considered in the base case model was two years. This time horizon was chosen to reflect the duration of the longest trial explored in the clinical review for maintenance of remission. In addition, the GDG considered that other treatment pathways not captured in the model could arise over a longer time horizon time, for example when treating patients that have frequent relapses. Hence, interpreting the results based on a longer time horizon could be inappropriate. However, the effect of a longer time horizon on the model results was explored in a sensitivity analysis.

5.2.2.2 Approach to modelling

5.2.2.2.1 Model structure

A Markov model was constructed in which, the QALY gain is driven by the amount of time people spend in the remission and active disease (relapse) states.

The trials included in the clinical review reported data on the number of relapses while on maintenance treatment. In addition, some of the trials reported data on the number of withdrawals from treatment. The available data informed the combined NMA, which provided estimates of probabilities of withdrawing from treatment and relapsing from maintenance treatment. The probability of relapse was conditional on not having withdrawn from maintenance treatment. Treatment effects in this economic model were based on these two outcomes - withdrawals and relapses.

A cycle length of two months was chosen to reflect the duration of the treatment of patients who are undergoing induction treatment for a flare. In any 2-month cycle, patients could remain in remission or experience a relapse. Patients who experienced a relapse were treated with the cost effective treatment strategy derived from the induction of remission economic model, described in section 5.1. Briefly, the strategy involved outpatient treatment with a high induction dose of oral ASA. In the event of failure to respond to this therapy, treatment was escalated as follows: high induction dose of oral ASA + beclometasone, followed by prednisolone. If the flare persisted, patients were treated as inpatients and received intravenous drug therapy which could be with either steroids or ciclosporin. Finally, lack of response to intravenous therapy resulted in patients having surgery.

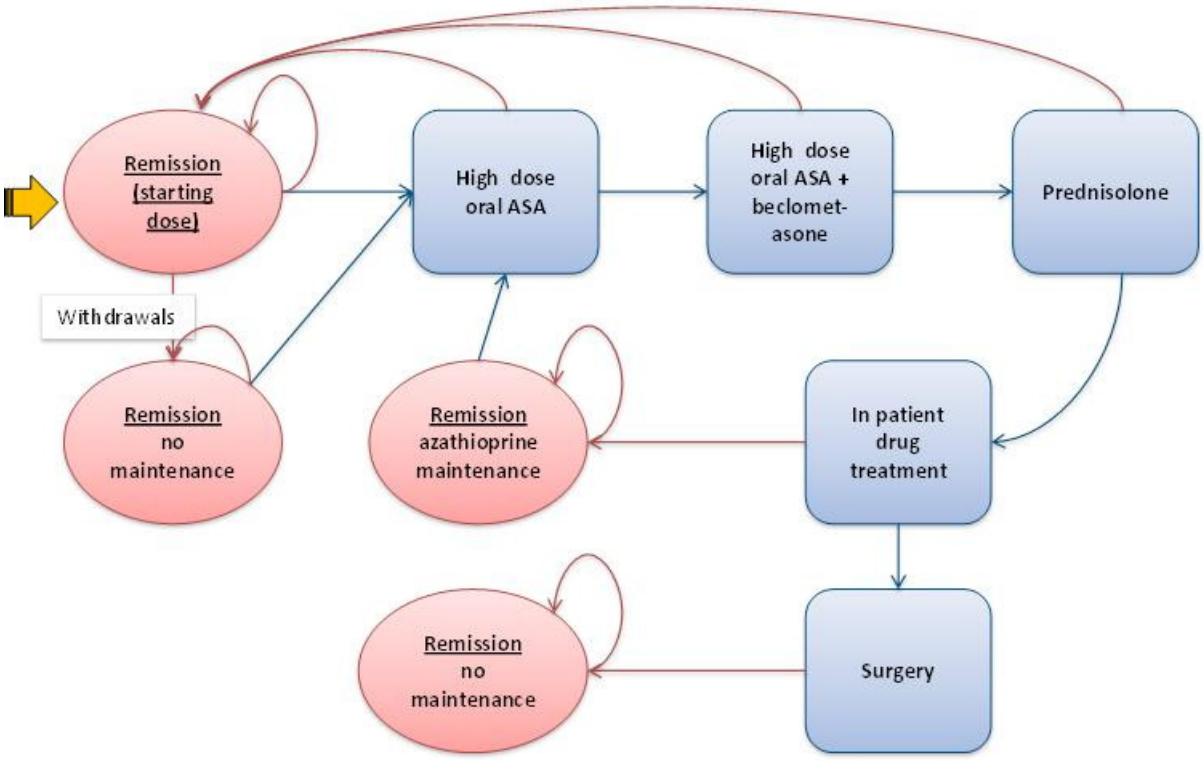
There were three options modelled for patients who went into remission after an outpatient flare. They could receive no treatment or they could be placed on either a low dose oral ASA or high dose oral ASA maintenance therapy as outlined in section 5.2.2.1.1. Inpatients that went into drug-induced remission were placed on azathioprine maintenance therapy while inpatients that had

surgically-induced remission remained in remission for the rest of the model and were not on any maintenance treatment. All patients in remission (except surgical remission) had a probability of relapsing.

Two Markov model structures were developed to describe the pathway of treatment. This was necessary as the treatment pathway varied depending on what maintenance treatment patients received after a flare. For all comparators, it was assumed that patients who withdrew from treatment remained in remission for the duration of the cycle. In the next cycle however, their risk of relapse was similar to those on no maintenance treatment.

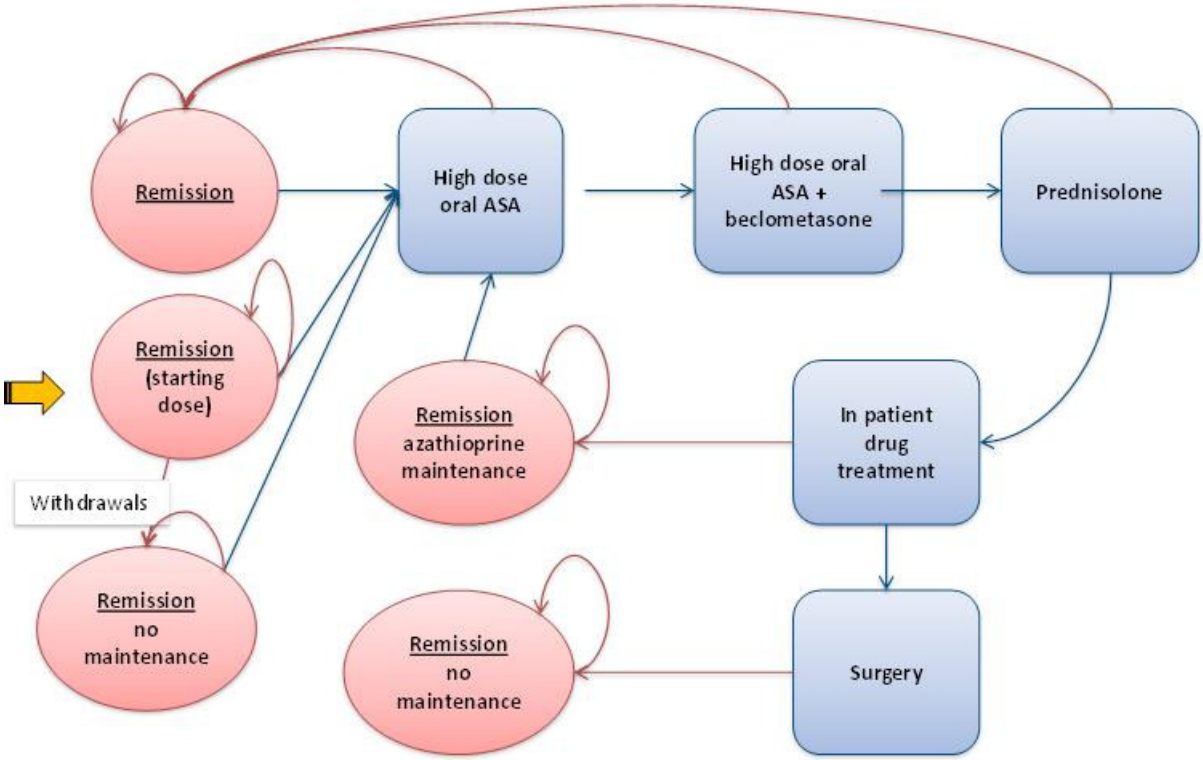
The first model structure shown in Figure 331 is relevant for comparators 1, 4 and 6 as described in section 5.2.2.1.1. Based on this, patients entered the model on one of the following options - no maintenance, low dose oral ASA or high dose oral ASA. In the event of a flare, they were treated as described above and following remission, they returned to the same maintenance regimen with which they entered the model.

Figure 331: Markov model structure for comparators 1, 4 and 6



The second model structure shown in Figure 332 is relevant for comparators 2, 3 and 5 as described in section 5.2.2.1.1. Based on this, patients entered the model on either no maintenance or low dose oral ASA. In the event of a flare, they were treated as described above but returned to a maintenance regimen different to that with which they entered the model.

Figure 332: Markov model structure for comparators 2, 3 and 5



5.2.2.3 Uncertainty

5.2.2.3.1 Probabilistic analysis

The model was built probabilistically to take account of the uncertainty around parameter point estimates. In order to do this, probability distributions based on error estimates from data sources, for example the standard error around a point estimate, were defined for each model input. When the model was run, a value for each input was randomly selected from its respective probability distribution. This was done repeatedly – 1000 times and results were summarised. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using the methods as described by Koehler and colleagues[69]. It is set to ensure that the Monte Carlo error is not more than 5% of the standard error for these parameters. The types of distribution used in the model are described in Table 71.

Table 71: Distributions used in the model

Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Cost and resource use	Gamma	Bounded at 0. Derived from mean and standard error	α = (mean/SEM)2 λ = mean/SEM2
Resource use	Triangular	Derived from expert opinion or reported in data source.	Min = minimum value Likeliest = mean Max = maximum value
Treatment effects, utility weights and reference costs	Lognormal	Bounded at 0. Derived from log (mean) and standard error.	μ = ln(meanRR) SD(μ) = (ln[UpperCI] – ln[lowerCI])/1.96*2

5.2.2.3.2 Uni- and multi-variate sensitivity analysis

Uni-variate (single variable) sensitivity analyses were conducted in order to test the robustness of model results to changes in key parameters. In one way sensitivity analysis, one parameter is varied while all other parameters are kept constant and the effects of changing this parameter on model results are explored. The analyses are described in Table 89. A multi-variate (multiple variable) sensitivity analysis was also conducted where more than one parameter was varied while other parameters were kept constant. The analysis is described in Table 90.

5.2.2.4 Model inputs

5.2.2.4.1 Summary table of model inputs

People in remission

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the BNF[63], drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs were validated by the GDG. Summaries of the model inputs used in the base-case analysis are provided in Table 72, Table 73 and Table 74. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 72: Summary of model inputs: clinical probabilities of withdrawal and relapse conditional on non-withdrawal (per cycle)

Variable	Probability of withdrawal	Probability of relapse conditional on non-withdrawal
No treatment	6.2%	13.3%
Low dose oral ASA	9.7%	6.8%
High dose oral ASA	7.4%	5.1%
Azathioprine	-	5.9%

Source: clinical review and NMA

Table 73: Summary of model inputs: utility weights

Variable	Estimate	Range	Reference
Remission on no maintenance treatment	0.940	0.937-0.943	Assumption
Remission on maintenance treatment	0.940	0.937-0.943	Poole et al [103]
Active disease (outpatient)	0.775	0.751-0.800	Poole et al [103]
Active disease (inpatient)	0.660	0.595-0.725	Poole et al [103]
Post-surgery	0.840	0.800-0.930[(a)]	Yen et al[137]

(a) Different from value used in the study. Value was chosen to ensure consistency with other utility scores used in the model.

Table 74: Summary of model inputs: cost inputs

Variable	Cost	Source
Drugs (per 2 month cycle)		

Variable	Cost	Source
Low dose oral ASA	£49.41	MIMS[1], Drug tariff[97]
High dose oral ASA	£100.11	MIMS[1], Drug tariff[97]
Azathioprine	£40.88	MIMS[1],
Tests		
Full blood count	£3.00	NHS reference costs[28] (code DAP823)
Renal and liver function tests	£1.00	NHS reference costs[28] (code DAP841)
TPMT	£26.00	Crohn's guideline[93]
Patient weight to calculate drug costs	77.9kg	National average body weight for UK (Crohn's guideline)[93]
Consultations (per hour)		
Consultant Gastroenterologist	£137.00	PSSRU[23]
General practitioner	£127.00	PSSRU[23]
IBD nurse specialist	£53.00	PSSRU[23]
Telephone consultation with IBD nurse specialist	£23.00	Payments by results guidance 2009-10[29]
Specialist registrar	£59.00	PSSRU[23]
Weekly consultation costs for patients in remission	£1.38	Calculation

People in relapse

The costs and probabilities associated with induction treatments for people in relapse are those associated with the optimal strategy in the induction of remission model and can be found in the induction of remission model write-up (section 5.1).

5.2.2.4.2 Baseline events (withdrawal and relapse)

Baseline risks were pooled from the placebo arms of RCTS included in the clinical review by using the generic inverse variance method. This provided the baseline log odds of withdrawals and log hazard of relapse conditional on non-withdrawal. The results are presented in Table 75.

Table 75: Baseline events

Treatment	Odds of withdrawal (log scale)	risk of relapse conditional on non-withdrawal (log hazard)
No treatment (Placebo)	-0.749	0.016

5.2.2.4.3 Relative treatment effects (withdrawal and relapse)

Treatment-specific probabilities for withdrawal and relapse conditional on non-withdrawal were obtained from the combined NMA conducted. A brief outline of the methods can be found below with the full methodology reported in Appendix I.

A logistic regression NMA was conducted to obtain estimates on the probability of withdrawal associated with a particular treatment. For estimates of relapse conditional on non-withdrawal, a specific NMA methodology termed a multi-statistic evidence synthesis[135] was conducted. This was used as relevant trials that reported relapse data presented them as either hazard ratios or

cumulative count statistics. The methodology allowed both of these outputs to be combined in a single analysis and for the treatment effects to be produced on a log hazard scale.

As relapse was made conditional on non-withdrawal, treatment effects for the model had to be accounted for such that the number of withdrawals and relapses could not exceed the number of people. This was relevant for trials reporting cumulative count statistics. The calculation was done by removing the number of withdrawals from the denominator when entering data for relapses into WinBUGS. The calculation is described in Equation 1. The NMA results are shown in Table 76.

Equation 2- Calculating probability of relapse conditional on non-withdrawal

$$\boldsymbol{P(R|W^c) = \frac{P(R)}{1 - P(W)}}$$

Where:

$P(R|W^c)$ = probability of relapse conditional on non-withdrawal

P(R) = probability of relapse

P(W) = probability of withdrawal

Table 76: Estimates of treatment effects from NMA

Treatment	Odds of withdrawal (log scale)	risk of relapse conditional on non-withdrawal (hazard ratio)
Low dose ASA	0.580	0.490
High dose ASA	0.214	0.366

The baseline effects shown in Table 6 were transformed to 2-month cycle probabilities. In addition, the baseline effects were adjusted by the treatment effects in Table 7 and transformed to 2-monthly probabilities as shown in Note: 2 months was expressed in terms of weeks to give a value of 8.66

Table 77. The transformation to two-month probabilities is described in Equation 3.

Equation 3: Transformation to two-month probabilities

$$\boldsymbol{p_{2month} = 1 - \exp[-(-\ln(1 - p_{1\,week})) * (8.66)]}$$

Note: 2 months was expressed in terms of weeks to give a value of 8.66

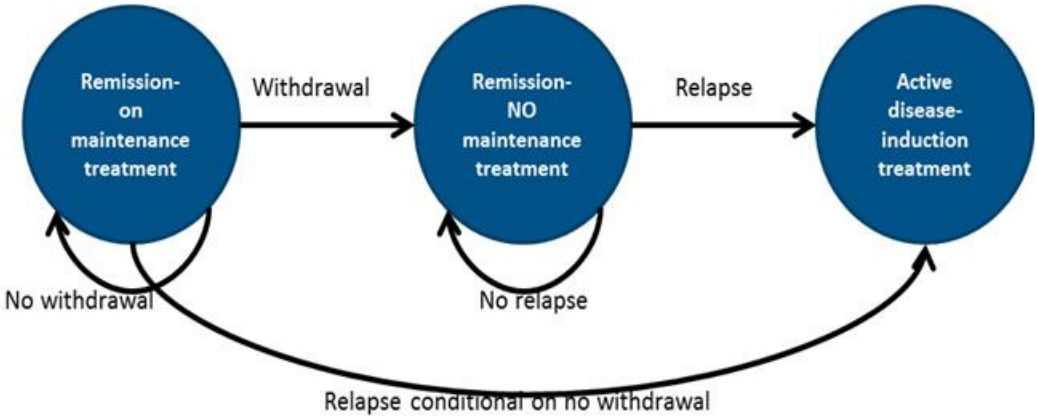
Table 77: Absolute probabilities per two-month cycle

Treatment	Probability of withdrawal	Probability of relapse conditional on non-withdrawal
No treatment	6.3%	13.3%
Low dose ASA	9.7%	6.8%
High dose ASA	7.4%	5.1%

People who did not withdraw from treatment relapsed according to the probabilities shown in Table 77 and moved into the active disease health states where they received treatment to induce remission.

People who withdrew from treatment remained in remission for the duration of the cycle. In the next cycle, they could remain in remission or have a probability of relapse similar to people on no treatment as shown in Table 77. This pathway is shown in Figure 333.

Figure 333: Pathway for patients withdrawing from treatment



Possible inconsistencies with the withdrawal data were noted. There was a higher probability of withdrawals from low dose oral ASA compared to high dose oral ASA. This could be due to people withdrawing from treatment for reasons other than adverse events. A sensitivity analysis was conducted where the probability of withdrawal from both low and high dose oral ASAs were set to the same value. This is described in Table 89.

Azathioprine maintenance

The clinical data on having a relapse while on azathioprine was obtained from Hawthorne 1992[55]. In the study, patients were randomised to either azathioprine (10-150mg) or placebo and followed up for 1 year. No withdrawals due to adverse events were reported. The GDG considered that since azathioprine maintenance was a secondary health state in the model, this paucity in data would not have a major influence on the results. The probability of relapse over a 2-month cycle was 5.9%.

5.2.2.4.4 Utilities

For economic evaluation, a specific measure of Health Related Quality of Life (HRQoL) known as utility is required to calculate Quality Adjusted Life Years (QALYs). Utilities indicate the preference for health states on a scale from 1 (perfect health) to negative infinity. Death in this model is considered to have a utility of 0. The NICE reference case[94] specifies that the preferred utility assessment tool is the EQ-5D instrument. The utilities used in the model were obtained from two studies[103],[137] described in Table 78.

Table 78: Utilities in the model

Name	Description	Values
Poole[103]	Ulcerative colitis disease activity index (UCDAI) scores and EQ5D scores were collected from 126 patients enrolled in a trial comparing oral and topical mesalazine with oral mesalazine alone. 92% of patients have mild/moderate UC while 8% had severe UC. An algorithm was developed to predict EQ5D scores based on individual abbreviated-UCDAI items. The algorithm was used to predict EQ5D scores for patients with differing UC severities enrolled in	Remission: 0.940 Mild/moderate disease: 0.775 Severe relapse: 0.660

Name	Description	Values
	the Phase IV PODIUM (Pentasa once daily in ulcerative colitis for maintenance of remission) study. In the PODIUM study, 359 patients were in remission at baseline. At 12 months, 73.8% were in remission, 22.6% were in mild to moderate relapse and 3.6% were in severe relapse.	
Yen[137]	The health states modelled were assigned utilities based on disease severity. The utilities were derived from various studies using the time trade off method. Some assumptions were made based on similarities with Crohn's disease.	Post-colectomy = 0.840

In order to capture the change in quality of life between the different health states modelled, utility scores were assigned as shown in Table 79. It was assumed that the utilities of being in remission on no maintenance treatment and on maintenance treatment were the same due to lack of relevant data.

Table 79: Health state utilities

Variable	Estimate	Range	Source
Remission on no maintenance treatment	0.940	0.937-0.943	Assumption
Remission on maintenance treatment	0.940	0.937-0.943	Poole et al [103]
Active disease (outpatient)	0.7750	0.751-0.800	Poole et al [103]
Active disease (inpatient)	0.660	0.595-0.725	Poole et al [103]
Post-surgery	0.840	0.800-0.930[(a)]	Yen et al[137]

(a) Different from value used in the study. Value was chosen to ensure consistency with other utility scores used in the model.

5.2.2.4.5 Resource use and cost

People in relapse

The drug and consultation costs for patients in relapse are show in Table 80. For more detailed information pertaining to induction of remission, see the induction of remission model write-up (section 5.1).

Table 80: Costs for people in relapse

Variable	Cost	Source
Course of high dose oral ASA[(a)]	£188.05	MIMS[1], PSSRU[23]
Course of high dose oral ASA + oral beclometasone[(a)]	£146.82	MIMS[1], PSSRU[23]
Course of prednisolone[(a)]	£83.37	MIMS[1], PSSRU[23]
Inpatient treatment	£2464.20	NHS reference costs[28](code FZ37G, FZ37H, FZ37I, FZ37J)
Surgery	£7404.44	NHS reference costs[28] (code FZ08A, FZ08B)

(a) Includes consultations

Please note that the detailed information in the section below is applicable to people in remission health states.

People in remission

1. Consultations

The GDG provided estimates on the frequency of consultations and the average length of consultation time that people in remission would receive on an annual basis. These consultations are regardless of the treatment patients are taking. Unit costs were obtained from the PSSRU[23] and adjusted by the consultation time to estimate average weekly costs of consultations. It was assumed that only 80% of patients would utilise these services. The inputs are summarised in Table 81.

Table 81: Consultations for people in remission

Type of consultation	Annual frequency	Length of consultation (minutes)	Cost per hour[(a)]
Consultant gastroenterologist	One per year (HALF of all people)	20	£137
General practitioner	One per year (all people)	17.2[(a)]	£127.00
IBD nurse specialist	One per year (HALF of all people)	20	£53.00[(b)]
Telephone consultation with IBD nurse specialist	One per year (HALF of all people)	10	£23.00
Specialist registrar	One per year (HALF of all people)	20	£59.00

(a) Source: PSSRU[23]
(b) Payments by results guidance 2009-10[29]

2. Drugs

Mesalazines, such as Mesren and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment on their relative efficacy. Therefore, for mesalazine preparations, only those addressed in the clinical review were used to inform drug costs in the model. The average costs of low dose and high dose oral ASAs were based on costs of the individual drugs and dose ranges described in described in Table 70. Unit costs were obtained from the drug tariff[97] and BNF[63]. The drugs included in the cost calculations are listed in Table 82, Source: MIMS[1] and GDG

Table 83 and Source: MIMS[1] and GDG

Table 84.

Table 82: Low dose oral ASA costs in the model

Cost item	Daily dose (grams)	Pack size	Cost per pack (£)	Cost per day (£)	Weekly cost (£)
Pentasa SR Tab 500mg	2	100	30.74	1.23	8.61
Mezavant XL G/R Tab 1.2g	1.2	60	62.44	2.08	14.57
Salofalk G/R Tab 500mg	1.5	100	32.38	0.97	6.80
Salofalk M/R G/R Granules 1.5g	1.5	60	48.85	0.81	5.70
Asacol M/R E/C Tab 400mg	1.2	90	29.41	0.98	6.86
Sulfasalazine E/C Tab 500mg	2	100	20.54	0.82	5.75
Sulazine E/C Tab 500mg	2	112	14.83	0.53	3.71

Cost item	Daily dose (grams)	Pack size	Cost per pack (£)	Cost per day (£)	Weekly cost (£)
Sulfasalazine Tab 500mg	2	112	8.16	0.29	2.04
Salazopyrin En-Tab 500mg	2	112	6.97	0.25	1.74
Salazopyrin Tab 500mg	2	112	8.43	0.30	2.11
Dipentum Tab 500mg	1	60	21.18	0.71	4.94
Colazide Capsules 750mg	3	130	30.42	0.94	6.55
Average costs per cycle			**£49.41**		

Source: MIMS[1] and GDG

Table 83: High dose oral ASA costs in the model

Drug name	Daily dosage (grams)	Pack size	Cost per pack(£)	Cost per day(£)	Weekly cost(£)
Pentasa SR Tab 500mg	4	100	30.74	2.46	17.21
Mezavant XL G/R Tab 1.2g	2.4	60	62.44	2.08	14.57
Salofalk G/R Tab 500mg	3	100	32.38	1.94	13.60
Salofalk M/R G/R Granules 1.5g	3	60	48.85	1.63	11.40
Salofalk M/R G/R Granules 1g	3	50	28.74	1.72	12.07
Asacol M/R E/C Tab 400mg	2.4	90	29.41	1.96	13.72
Sulfasalazine E/C Tab 500mg	4	100	20.54	1.64	11.50
Sulazine E/C Tab 500mg	4	112	14.83	1.06	7.42
Sulfasalazine Tab 500mg	4	112	8.16	0.58	4.08
Salazopyrin En-Tab 500mg	4	112	6.97	0.50	3.49
Salazopyrin Tab 500mg	4	112	8.43	0.60	4.22
Dipentum Tab 500mg	2	60	21.18	1.41	9.88
Colazide Capsules 750mg	6	130	30.42	1.87	13.10
Average costs per cycle			**£100.11**		

Source: MIMS[1] and GDG

Table 84: Azathioprine costs in the model

Drug name	Daily dosage (mg/kg)	Pack size	Cost per pack(£)	Cost per day[(a)] (£)	Weekly cost(£)
Azathioprine 25mg Tab	2.5	28	6.02	1.67	11.72
Azathioprine 50mg Tab	2.5	56	5.04	0.35	2.45
Imuran 25mg Tab	2.5	100	10.99	0.86	5.99

Drug name	Daily dosage (mg/kg)	Pack size	Cost per pack(£)	Cost per day[(a)] (£)	Weekly cost(£)
Imuran 50mg Tab	2.5	100	7.99	0.31	2.18
Average costs per cycle			**£40.88**		

Source: MIMS[1] and GDG
(a) calculated based on an average patient weight of 77.9kg

Drug-specific tests

Drug-specific tests were based on the recommendations in the BNF[63] and were verified by the GDG. Patients on maintenance treatment on either low dose or high dose oral ASA had 2 renal function tests and 2 full blood counts in the first year and then one set of tests annually. Patients on maintenance with azathioprine were assumed to have one thiopurine methyltransferase (TPMT) assay prior to initiation of treatment, as well as full blood counts, liver and renal function tests on a regular basis. The frequency of tests while on azathioprine decreased after the first year. These tests are summarised in Table 85 and Table 86.

Table 85: Tests for people on low dose or high dose oral ASAs

Type of test	Unit cost	Year one	Year 2	Source
Full blood count	£3	2 tests	1 test	NHS reference costs[28] (code DAP823)
Renal function test	£1	2 tests	1 test	NHS reference costs[28] (code DAP841)

Table 86: Tests for people on azathioprine

Type of test	Unit cost	Year one	Year 2	Source
Full blood count	£3	12 tests	4 tests	NHS reference costs[28] (code DAP823), BNF 61[63]
Renal function test	£1	12 tests	4 tests	NHS reference costs[28] (code DAP841), BNF 61[63]
Liver function test	£1	12 tests	4 tests	NHS reference costs[28] (code DAP823), BNF 61[63]
TPMT assay	£26	1 test	-	Crohn's guideline[93]

Summary of health state costs

The total costs attributed to each health state comprised of the costs of drugs, tests and consultations. The costs per two-month cycle are shown in Table 87.

Table 87: Health state costs

Health state	Costs	Source
Remission on no maintenance treatment	£11.91	Calculations
Remission on low dose oral ASA maintenance treatment	£62.65	Calculations
Remission on high dose oral ASA maintenance treatment	£113.35	Calculations
Remission on azathioprine maintenance treatment	£67.11	Calculations

5.2.2.4.6 Computations

The mean cost and effectiveness of the competing strategies were calculated using Microsoft Office Excel 2007.

5.2.2.4.7 Calculating QALYs

In order to calculate the QALYs associated with a given treatment, in each cycle, the number of people in each health state was multiplied by the utility weight associated with that health state and divided by an adjustment factor to reflect the cycle length. A worked example of the utility calculation is shown In Table 88; please note this is a simplified calculation as the full calculation would take account of all the health states shown in Table 79.

Table 88: Example calculation of QALYs

	Remission	Active disease (outpatient)
Number of people in health state	720	280
Utility weight	0.94	0.775
QALYs per patient (over a 2 month cycle)	$\frac{720 \times 0.94}{1000} \times \frac{2}{12} = 0.113$	$\frac{280 \times 0.775}{1000} \times \frac{2}{12} = 0.036$

The total QALYs for the 2 month cycle described above would be 0.113 + 0.036 = 0.149. These QALY contributions are then aggregated over the two-year model time horizon to calculate the total number of QALYs associated with each treatment.

5.2.2.4.8 Probabilistic analysis in the model

In the probabilistic analysis, distributions were assigned to treatment effects, utilities and where possible, costs as described in Table 71. This was done to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs. Please see the induction of remission model write-up for more details on how inputs pertaining to induction of remission were made probabilistic.

Treatment effects:

To capture the uncertainty in treatment effects, a sample of 1000 random sets of treatment effects was taken from the NMA using the CODA function in WinBUGS. This has the advantage of preserving the correlation between variables, which would not be accounted for if they were sampled from their individual distributions. For the probabilistic analysis, in each simulation, a random set of treatment effects was chosen from the sample using random number generation.

Reference costs:

Costs of tests, in-patient treatment and surgery were obtained from NHS reference costs. In order to assign a distribution to reference costs, it was assumed that they followed a lognormal distribution and the interquartile range was used to calculate an approximate standard error on the log scale. The calculation is explained below.

Let $\boldsymbol{X}$ be the cost assigned to a distribution to, i.e. $\ln(\boldsymbol{X}) \sim \boldsymbol{Normal}(\boldsymbol{\mu}, \boldsymbol{\sigma^2})$

Let M be the mean associated with the cost.

Let $\boldsymbol{IQR}$ be the interquartile range associated with the cost.

Note that for normally distributed data:

$$IQR \approx 1.35\sigma$$

And noting that the standard error $\boldsymbol{s}$, is related to the standard deviation by:

$$s = \frac{\sigma}{\sqrt{n}}$$

Then the standard error on the log scale can be calculated as:

$$\sigma = \frac{\ln(IQR)}{1.35 \times \sqrt{n}}$$

And therefore random draws from the distribution can be taken:

$$\ln(X) \sim Normal\left(ln\left(\mu - \frac{\sigma^2}{2}\right), \left(\frac{\ln(IQR)}{1.35 \times \sqrt{n}}\right)^2\right)$$

Utilities:

Utilities were sampled probabilistically by assigning lognormal distributions to utility decrements as described in (ref Briggs). Normal distribution parameters were converted to lognormal parameters by method of moments, as defined below:

Let $E[X]$ and $Var[X]$ be the mean and variance respectively, of the utility decrement U

Then the parameters of the lognormal distribution, μ and σ^2 are found by:

$$\mu = \ln(E[X]) - \frac{\ln\left(1 + \frac{Var[X]}{E[X]^2}\right)}{2}$$

$$\boldsymbol{\sigma^2 = \ln\left(1 + \frac{Var[X]}{E[X]^2}\right)}$$

5.2.2.4.9 Calculating cost-effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in terms of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NMB is used to identify the optimal strategy in the probabilistic analysis simulations.

Let $\mathrm{C_t}$ and $\mathrm{Q_t}$ denote the mean costs and mean QALYs respectively, associated with a given treatment. Then the mean net monetary benefit $\mathrm{NMB_t}$ is calculated as:

$$\mathrm{NMB_t} = (20{,}000 \times \mathrm{Q_t}) - \mathrm{C_t}$$

Where £20,000 per QALY represents the cost-effectiveness threshold in the NICE reference case.

This net benefit is calculated for each of the 1000 simulations in the probabilistic analysis. This means that the probability that a given treatment would be optimal can be estimated based on the number of times it has the highest net monetary benefit.

However, the strategy that is optimal overall is the one that has the highest net monetary benefit calculated using the mean costs and QALYs, where means were the average of the 1,000 simulated estimates.

5.2.2.5 Sensitivity analyses

The sensitivity of the results to changes to inputs and assumptions was tested by conducting four uni-variate sensitivity analyses as described in Table 89. The analyses were conducted deterministically.

Table 89: Uni-variate sensitivity analyses in the model

Sensitivity analysis	Description	Value in base case	Value or range in sensitivity analysis
SA1: Time horizon	Time horizon increased	Two years	Five years
SA2: QALY discount rate	QALY discount rate decreased	3.5%	1.5%
SA3: High baseline risk	It was decided to increase the baseline risk for relapse to reflect a cohort that was more prone to flares. The aim was to determine what treatment sequence would be appropriate in this scenario.	14.2%	90%
SA4: Low baseline risk	It was decided to decrease the baseline risk for relapse to reflect a cohort less prone to flares. The aim was to determine what treatment sequence would be appropriate in this scenario.	14.2%	10%
SA5: Withdrawal rates	The withdrawal rates from low dose and high dose ASA were set to the same values to account for uncertainty in the withdrawals data.	Low dose ASA: 7.4% High dose ASA: 9.7%	Low dose ASA: 9.7% High dose ASA: 9.7%

One multi-variate sensitivity analysis was conducted deterministically to address the effects of ASA costs on the model results. The analysis is described in Table 90.

Table 90: Multi-variate sensitivity analysis in the model

Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
Drug costs	In the base case, the daily costs of oral ASAs were based on an average of individual ASA preparations. The GDG was aware of the costs differences between different ASA preparations. This SA was conducted to capture the effect of ASA drug costs on the model results.	Daily cost of low dose oral ASA = £0.82 Daily cost of high dose oral ASA = £1.65	The daily costs of ASAs were varied from in £0.20 increments.

5.2.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of the model formulae and calculations. The model parameters and results were also assessed against the content of this appendix.

5.2.2.7 Interpreting results

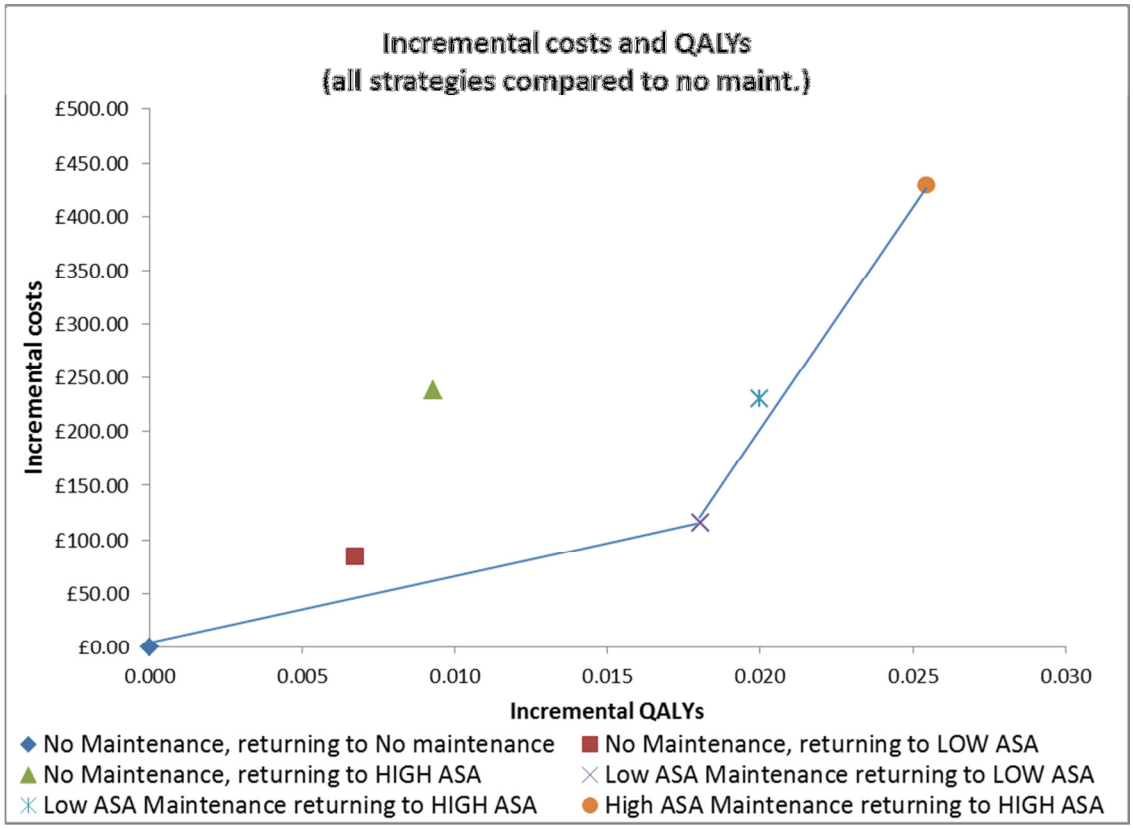
The strategy with the highest mean net monetary benefit is the one that should be recommended[35] though the uncertainty around costs and QALYs should also be taken into consideration. Due to lack of data we were unable to explicitly capture the disutility of treatment-specific adverse events. This should be taken into consideration when interpreting the results.

5.2.3 Results

5.2.3.1 Base case results

In the base case, model inputs were set as shown in section 5.2.2.4 and the model was run probabilistically. Figure 334 shows the incremental increase in costs and QALYs when all strategies are compared to the no maintenance returning to no maintenance strategy. Note that the line on the graph represents the non-dominated options, this means the options that are more costly but also more effective and under the £20,000 per QALY gained threshold. The graph shows that the low maintenance returning to low maintenance strategy is the cost effective option because while it is more costly than no treatment it is also considerably more cost effective. The high maintenance returning to high maintenance strategy is not considered cost effective because, while it is more effective than the low maintenance returning to low maintenance strategy, this gain does not justify the increased cost as incremental cost-effectiveness ratio of £42,574 was calculated. This is significantly greater than the £20,000 per QALY cost-effectiveness threshold defined by NICE.

Figure 334: Incremental cost-effectiveness compared to no treatment



Cost-effectiveness in the base case (per patient)

The probabilistic results allowed a ranking of the net monetary benefit to be developed and also showed the probability of an intervention being cost effective out of 1000 simulations. The cumulative ICERs for the 1000 simulations were plotted to check the stability of the ICERs. The ICERs were stable after approximately 200 simulations. Table 91 shows the breakdown of the results. The low maintenance returning to low maintenance strategy had the highest NMB and was cost effective in 61% of the simulations. The high maintenance returning to high maintenance strategy was cost effective in 30% of cases. This shows that while the low maintenance returning to low maintenance strategy is likely to be cost effective there is uncertainty about this result and there is a good possibility that high maintenance returning to high maintenance strategy could be cost effective. The uncertainty between these two options can be found in Figure 335. This figure shows that while in the majority of cases, the low maintenance returning to low maintenance strategy is in the top right hand quadrant of the cost-effectiveness plane and under the cost-effectiveness threshold, it is occasionally less cost effective than the high maintenance returning to high maintenance strategy (in the top left quadrant – more costly and less effective).

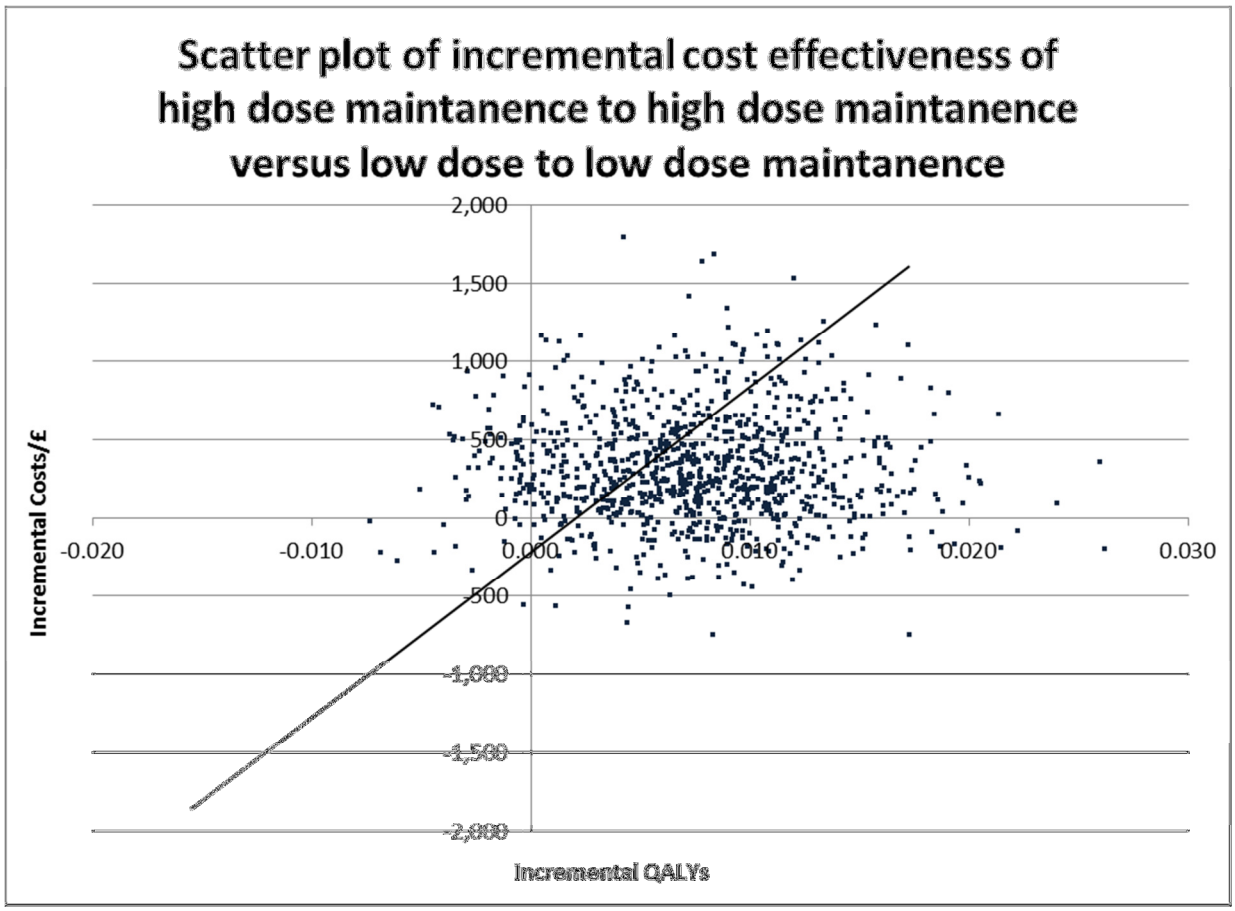
Table 91: Cost-effectiveness in the base case (per patient)

Comparator	Costs	QALYs	NMB[(a)]	NMB rank (95% confidence interval) [(a)]	Probability of being most cost-effective strategy	ICER compared to no maintenance
No maintenance returning to no maintenance strategy	£926	1.780	£34,670	5(1,6)	9%	comparator
No maintenance returning to low dose	£1,011	1.787	£34,720	4(2,6)	0%	£12,526

Comparator	Costs	QALYs	NMB[(a)]	NMB rank (95% confidence interval) [(a)]	Probability of being most cost-effective strategy	ICER compared to no maintenance
oral ASA strategy						
No maintenance returning to high dose oral ASA strategy	£1,165	1.789	£34,618	6(2,6)	0%	£25,596
Low dose oral ASA returning to low dose oral ASA strategy	£1,041	1.798	£34,916	1(1,6)	61%	£6,382
Low dose oral ASA returning to high dose oral ASA strategy	£1,157	1.800	£34,839	2(2,5)	0%	£11,534
High dose oral ASA returning to high dose oral ASA strategy	£1,356	1.805	£34,749	3(1,6)	30%	£16,909

(a) Using a willingness to pay threshold of £20,000 per QALY

Figure 335: Scatter plot to show the uncertainty around the incremental costs and effect between the high dose ASA returning to high dose ASA strategy and low dose ASA returning to low dose ASA strategy



In order to better understand the above results, a further break down can be found below.

Costs

Table 92 shows the total costs attributed to each comparator in the model. The total costs are calculated based on costs of drugs, tests, consultations, inpatient treatment and surgery. Over a two year horizon, the no maintenance retuning to no maintenance strategy has the lowest costs at £926.24 per patient. This is because the costs of maintenance treatment with ASAs are not a factor in this comparator.

Table 92: Mean costs in the base case (per patient)

Comparator	Drugs	Tests	Consultations	Inpatient	Surgery	Total
No maintenance returning to no maintenance strategy	£389.57	£1.30	£261.86	£219.93	£53.59	£926.24
No maintenance returning to low dose oral ASA strategy	£506.38	£3.42	£249.16	£202.02	£49.70	£1,010.69
No maintenance returning to high dose oral ASA strategy	£673.11	£3.56	£244.31	£195.39	£48.29	£1,164.66
Low dose oral ASA returning to low dose oral ASA strategy	£610.31	£6.33	£228.82	£157.90	£38.03	£1,041.38
Low dose oral ASA returning to high dose oral ASA strategy	£735.16	£6.43	£225.13	£153.08	£37.03	£1,156.83
High dose oral ASA returning to high dose oral ASA strategy	£969.86	£6.71	£215.22	£132.81	£31.83	£1,356.43

Outcomes

Table 93 shows the amount of time spent in remission and active disease for each comparator. Time in remission is made up of time spent while on no drug treatment and maintenance treatment. Time with active disease is made up of time spent while on induction treatment and surgery. This information was used to calculate the total QALYs for each strategy as described in section 5.2.2.4.7. The most effective comparator was the high maintenance returning to high maintenance strategy as 20.68 weeks were spent in remission and 3.31 weeks in active disease. This resulted in 1.805 QALYs over a two year time horizon.

Table 93: Mean clinical outcomes in the base case (per patient)

Comparator	Time on no maintenance treatment	Time on drug maintenance treatment	Total time in remission	Time on induction treatment	Time in Surgery	Total time with active disease	Total QALYs
No maintenance returning to no maintenance strategy	17.33	1.36	18.68	5.27	0.04	5.31	1.780
No maintenance returning to low dose oral ASA strategy	12.14	7.17	19.31	4.65	0.03	4.68	1.787

Comparator	Time on no maintenance treatment	Time on drug maintenance treatment	Total time in remission	Time on induction treatment	Time in Surgery	Total time with active disease	Total QALYs
No maintenance returning to high dose oral ASA strategy	12.62	6.74	19.36	4.60	0.03	4.63	1.789
Low dose oral ASA returning to low dose oral ASA strategy	5.67	14.92	20.59	3.38	0.02	3.40	1.798
Low dose oral ASA returning to high dose oral ASA strategy	5.97	14.66	20.63	3.34	0.02	3.36	1.800
High dose oral ASA returning to high dose oral ASA strategy	7.45	13.23	20.68	3.29	0.02	3.31	1.805

5.2.3.2 Sensitivity analyses

5.2.3.2.1 Uni-variate sensitivity analysis

One-way sensitivity analyses as described in Table 89 were conducted in order to test the robustness of model results. The analyses were conducted deterministically and the results are presented in Table 94. SA1 shows that over a 5 year time horizon, the low dose oral ASA returning to low dose oral ASA strategy remained the cost effective option. This was also the same result in SA2 which looked at the impact of a 1.5% QALY discount rate on the analysis. SA3 looked at the impact of a higher baseline risk on the base case results. A higher baseline risk suggests that patients are more likely to have a relapse. In this scenario, the high dose oral ASA returning to high dose oral ASA strategy was the cost effective option. This can be interpreted to mean that it is cost effective to maintain patients who are more prone to relapses on a high dose ASA due to it being more efficacious than other comparators. Cost gains are made by preventing downstream costs of more expensive drug treatment and hospitalisations. SA4 looked at the impact of a lower baseline risk on the base case results. A lower baseline risk suggests that patients are less prone to relapses. In this scenario, the no maintenance returning to no maintenance strategy was the cost effective option. This means that for patients who do not frequently relapse, it is cost effective to treat them only when they have a flare. SA5, which addressed the uncertainty in withdrawal rates did not change the conclusions of the base case analysis.

Table 94: Uni-variate sensitivity analyses–mean net monetary benefit per patient*

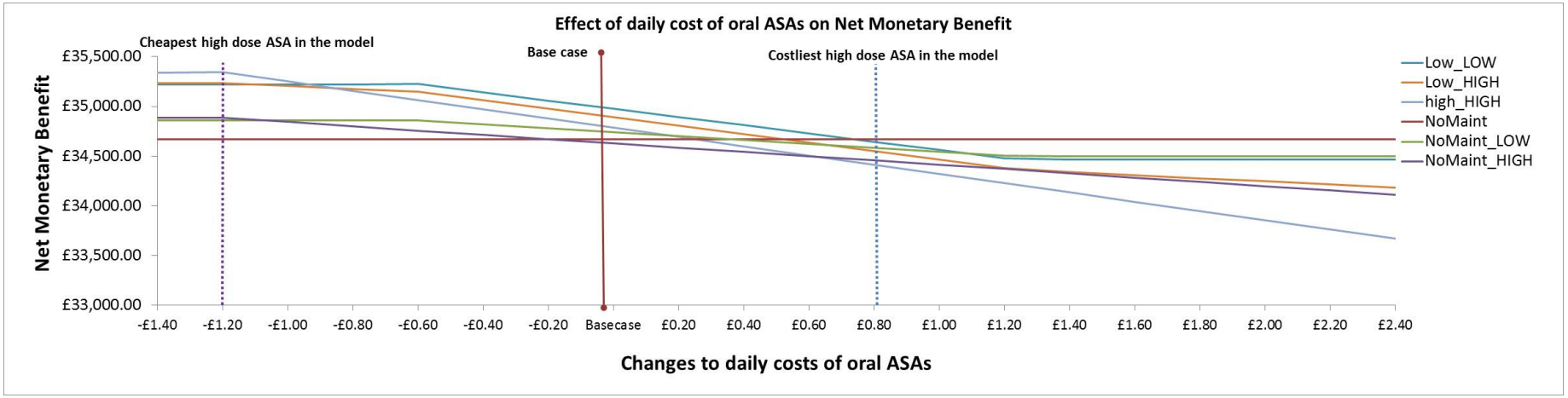
Comparator	Base case	SA1	SA2	SA3	SA4	SA5
No maintenance returning to no maintenance strategy	£34,675	£82,207	£35,009	£32,839	£36,450	£34,675
No maintenance returning to low dose oral ASA strategy	£34,751	£82,579	£35,086	£33,240	£36,425	£34,751

Comparator	Base case	SA1	SA2	SA3	SA4	SA5
No maintenance returning to high dose oral ASA strategy	£34,640	£82,294	£34,975	£33,211	£36,391	£34,645
Low dose oral ASA returning to low dose oral ASA strategy	£34,988	£82,827	£35,325	£33,592	£36,226	£34,988
Low dose oral ASA returning to high dose oral ASA strategy	£34,906	£82,573	£35,242	£33,561	£36,204	£34,909
High dose oral ASA returning to high dose oral ASA strategy	£34,807	£82,473	£35,143	£33,626	£35,839	£34,809

5.2.3.2.2 Multi-variate sensitivity analysis

One multi-variate deterministic analysis as described in Table 90 was conducted to assess the effect of daily costs of oral ASA on the model results. Figure 336 shows the change to the NMB for each comparator as daily costs of ASAs are decreased or increased in £0.20 increments. The no maintenance returning to no maintenance strategy remained unchanged as it is not influenced by the costs of ASA maintenance treatment. Overall, the NMB for all comparators decreased as the costs of daily ASAs increased. If the cheapest high dose ASA identified in the model was used, the high dose oral ASA returning to high dose oral ASA strategy became the cost effective option. If the costliest high dose ASA identified in the model was used, the no maintenance to no maintenance strategy becomes favourable. These results are to be interpreted with caution as other ASAs are available whose costs have not been included in this analysis.

Figure 336: Effect of daily cost of oral ASAs on net monetary benefit



5.2.4 Discussion

5.2.4.1 Summary of results

The cost-effectiveness analysis shows that it is cost effective to use a low dose oral ASA to maintain remission in patients who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive ulcerative colitis. This analysis was based on a multi-statistic network meta-analysis conducted using RCT data, acquisition costs, PSSRU costs and NHS reference costs. The results were robust to sensitivity analysis conducted.

5.2.4.2 Limitations and interpretations

The model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. Limitations of the model which impact on the interpretation of the results are as follows:

- The costs and dis-utilities of drug-specific adverse events were not explicitly modelled due to lack of robust data. This means that the cost-effectiveness of oral ASAs may have been over-estimated although the magnitude is unknown as each individual ASA is likely to have a specific side-effect profile. The overestimation of the ICER would be greater for ASAs that have more serious side effects compared to those with less serious side effects. This introduces uncertainty around interpretation of the results.
- In the model, it is assumed that all relapses have the same severity. It is possible therefore that the induction treatment sequence may not be appropriate for all patients. This assumption may overestimate the cost-effectiveness of all comparators.
- Mesalazines, such as Mesren and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment on their relative efficacy. The GDG were unable to comment about the relative efficacy of these mesalazines hence caution should be exercised when generalising the results of this model.
- Patients who withdraw from treatment were assumed to still be in remission. This is a conservative approach. If withdrawal from treatment results in flare of disease, the cost-effectiveness of all comparators may have been overestimated in the model.
- Treatment adherence was assumed to be 100% in the model. The GDG however noted that this may not be the case in reality and measures to improve adherence are discussed elsewhere in the guideline.

5.2.4.3 Generalisability to other populations/settings

The analysis was based on data obtained from an adult population hence may not be generalizable to paediatric populations. This is especially important as the dose ranges of ASAs were based on adult doses. A model relevant to the paediatric population could not be constructed due to paucity of clinical data.

Relapses in the model are assumed to be mild to moderate initially. In reality, patients may experience greater severities of relapse which may necessitate treatment options different to those captured in the model. Similarly, other extents of UC such as proctitis have not been addressed and as such treatment options used in the model may not be applicable.

5.2.4.4 Comparisons with published studies

The results of relevant economic studies addressing this topic area have been summarised briefly in section 5.2.1.

Yen[137] assessed the cost-effectiveness of no maintenance therapy versus 5-ASA maintenance therapy in patients with mild to moderate UC. In the study, 5-ASA therapy was shown to increase the discounted QALYs per person yielding an incremental cost-effectiveness ratio (ICER) of £146,000/QALY. This result was sensitive to costs of ASA as the ICER decreased to £10,306/QALY when cheaper drug costs of sulfasalazine were used.

The comparators modelled in the study are similar to two comparators in this original economic analysis -the no maintenance, returning to no maintenance and low dose oral ASA returning to high dose oral ASA strategies. A major difference between two analyses is the cost of drug treatment. An ICER of £11,534/QALY was calculated when the two strategies were compared in our model. This is taking into account the fact that drug costs used in our model were closer to the sensitivity analysis values used in the Yen study. In addition, post-operative complications and costs have been modelled in the Yen study which could explain the differences in the results.

5.2.4.5 Conclusion and evidence statements

The original cost-effectiveness analysis conducted for this guideline suggests that low dose oral ASA is the most cost effective option to maintain remission in patients with left sided or extensive ulcerative colitis, although there is considerable uncertainty related to interpretation of the withdrawals data.

6 Appendix M: Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

6.1 Key future research recommendations (FRR)

6.1.1 FRR1 Induction of remission for people with moderate ulcerative colitis: prednisolone compared with aminosalicylates

Research question:

What is the clinical and cost effectiveness of prednisolone compared with aminosalicylates for the induction of remission for people with moderate ulcerative colitis?

Why this is important:

Currently, people with moderate active ulcerative colitis most frequently receive either aminosalicylates or prednisolone as treatment, but there is no direct trial evidence comparing these treatments. Therefore people may receive treatment that is either less effective (in terms of symptom reduction or resolution, quality of life or healing of the colonic mucosa) or associated with greater side effects (especially with prednisolone). This is an important question in children, but the use of steroids is more contentious in children and there may be greater reluctance to use them because of possible effects on growth and development. People with moderate exacerbations of ulcerative colitis would be recruited and randomised to receive either prednisolone plus a bone-protecting agent or high-dose aminosalicylates. Primary end-points should be clinical remission and endoscopic remission.

Criteria for selecting high-priority research recommendations:

PICO question	Population – children and adults with moderate active ulcerative colitis. Intervention – prednisolone Comparison – aminosalicylates Outcome – critical outcomes would include: clinical remission (time to remission); endoscopic remission; clinical improvement; quality of life.
Importance to patients or the population	Currently, patients with moderate active ulcerative colitis most frequently receive either aminosalicylates or prednisolone as treatment, but there is no direct trial evidence comparing these treatments. Therefore there is potential for patients to receive treatment that is either less effective in terms of symptom reduction or resolution, quality of life or healing of the colonic mucosa, or associated with greater side-effects – particularly when receiving prednisolone.
Relevance to NICE guidance	Future guidelines would be able to give clear guidance, based on direct evidence of which treatment is more appropriate.
Relevance to the NHS	Improved symptom control may reduce hospital attendances and GP and specialist nurse consultations. Reduced steroid use would result in reduced steroid related morbidity including those relating to osteoporosis.
National priorities	Appropriate use of systemically available corticosteroids, such as prednisolone, will help in the approach to growth and development in children and young people and reducing risks relating to osteoporosis.
Current evidence base	No direct comparisons between aminosalicylates and prednisolone exist. Guideline recommendations have been made on the basis of clinical experience, consensus, network meta-analysis and economic analysis (see chapter 5 and appendices I and L). The evidence base also lacks a way of differentiating

	between those with differing severity of attacks, but which still fall in the 'moderate' category as defined by Truelove and Witts, and described in chapter 5 of the guideline.
Equality	No current equality issues identified.
Study design	Randomised controlled, double blind trial, in which patients with moderate flares of ulcerative colitis are randomised to receive either prednisolone plus a bone protecting agent or high dose aminosalicylates. The effect of disease severity within this cohort should also be evaluable (for example by stratification using clinical or laboratory parameters). Clinical and endoscopic remission should be considered as co-primary end-points, and adverse events (particularly related to systemic corticosteroid effect), quality of life and cost-effectiveness should also be evaluated, including non-invasive measures of mucosal healing.
Feasibility	This would be feasible in a reasonable time frame and at a reasonable cost.
Other comments	There are additional issues (for example relating to growth and development) which would determine the place of corticosteroids in children and so a trial needs to take this into account. However, this remains an important question in children, as well as adults, and so children have been included in this research question and recommendation. The guideline comments on two additional areas of weakness in the evidence base. Firstly, Evidence for drugs used for maintenance of remission is not generally based on studies where people are randomised following an acute flare of the condition – which is the usual clinical situation in which such treatment is prescribed. Secondly, the guideline recommendations on second-line treatment uses information from studies where the drugs have actually been used first line. The study described above could therefore be usefully run in such a way that additional studies addressing these two, additional gaps could be run.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.2 FRR2 Induction of remission for people with moderate ulcerative colitis: prednisolone compared with beclometasone

Research question:

What is the clinical and cost effectiveness of prednisolone plus an aminosalicylate compared with beclometasone plus an aminosalicylate for induction of remission for people with moderate ulcerative colitis?

Why this is important:

Evidence exists about the effectiveness of beclometasone plus an aminosalicylate for induction of remission in people with moderate ulcerative colitis. It seems likely that any corticosteroid would have a similar effect to beclometasone (in combination with an aminosalicylate), but no evidence was available to confirm this. Prednisolone is cheap and readily available. Evidence to show comparable or better clinical and cost effectiveness of prednisolone plus an aminosalicylate compared with beclometasone plus an aminosalicylate would represent a significant cost benefit and potentially increased or at least similar clinical efficacy. The research should take the form of a double-blind randomised controlled trial. The outcomes should include patient satisfaction measures.

Criteria for selecting high-priority research recommendations:

PICO question	Population – people with moderate ulcerative colitis. Intervention – prednisolone+ ASA. Comparison – beclometasone + ASA.

	Outcome – critical outcomes would include: clinical remission (time to remission); endoscopic remission; clinical improvement; quality of life.
Importance to patients or the population	The importance of effective induction of remission is high due to the debilitating nature of the condition. Future guidance may recommend prednisolone + ASA as a clinically effective as well as cost effective option: the research is essential to inform future updates of key recommendations in the guideline.
Relevance to NICE guidance	Future NICE guidance may recommend prednisolone+ASA ahead of other combinations for induction in moderate ulcerative colitis
Relevance to the NHS	Prednisolone is approximately 50x cheaper than beclometasone (BNF Nov 12 equivalent doses). There would be a requirement to disseminate any updated guidance to stakeholders.
National priorities	If prednisolone is at least as effective in combination with ASA as beclometasone people would have an effective treatment. If it is more effective people would experience the benefit of better induction of remission either in terms of time to resolution and/or an extended period of remission
Current evidence base	The NICE Ulcerative Colitis Guideline Development Group systematic review found no evidence available regarding prednisolone+ASA as a treatment option.
Equality	The research has no equality issues.
Study design	The research to take the form of a double blind randomised controlled trial. The outcomes should include patient satisfaction measures.
Feasibility	No issues noted.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.3 FRR3 Induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids

Research question:

What are the benefits, risks and cost effectiveness of methotrexate, ciclosporin, tacrolimus, adalimumab and infliximab compared with each other and with placebo for induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids?

Why this is important:

The best drug treatment for people with subacute ulcerative colitis whose condition fails to respond to treatment with oral prednisolone (a systemic corticosteroid) is unclear. Without effective treatment the condition may deteriorate, and may lead to the person requiring hospital admission for intravenous corticosteroid treatment or even surgery. It is common clinical practice to offer treatment with methotrexate or a calcineurin inhibitor (ciclosporin or tacrolimus), but high-quality evidence to guide clinicians is lacking. The use of infliximab in such cases was not recommended by NICE in technology appraisal guidance 140. This question should be investigated by a multicentre randomised, placebo-controlled trial in adults in secondary care. Outcomes should include patient-centred outcome measures.

Criteria for selecting high-priority research recommendations:

PICO question	Population – people with subacute ulcerative colitis refractory to systemic steroids. Intervention – methotrexate, ciclosporin, tacrolimus, adalimumab, infliximab. Comparison – to each other and placebo.

	Outcome – critical outcomes would include: clinical remission (time to remission); endoscopic remission; clinical improvement; quality of life.
Importance to patients or the population	At present, individuals may be offered treatment with an ineffective drug and be exposed to significant adverse effects. Moreover, the underlying disease may progress decreasing quality of life and possibly leading to hospital admission or surgery.
Relevance to NICE guidance	The answer to this research question will determine future NICE guidance and change clinical practice. The research findings will generate new knowledge that will be of value to gastroenterologists throughout the UK.
Relevance to the NHS	The results may improve the out-patient management of individuals with subacute ulcerative colitis or proctitis and possibly avoid surgery. If these drugs are effective people would have fewer days off work or be admitted to hospital. There would be health benefits and cost benefits to the NHS and the wider economy.
National priorities	This question involves improving the care of individuals with a chronic illness in keeping with the National Service Framework for Long Term Conditions.
Current evidence base	The current evidence base is very small; there are only two low quality RCTs of tacrolimus as induction treatment. There are no RCTs for the use of methotrexate or ciclosporin in subacute ulcerative colitis or proctitis.
Equality	The research question has no particular equality issues.
Study design	Multi-centre randomised, placebo-controlled trial in adults in secondary care. Outcomes should include patient-centred outcome measures.
Feasibility	Strict entry criteria will be required. A clear definition of subacute colitis or proctitis will be needed. In view of the risks associated with these drugs (increased risk of infection; lung, liver and kidney damage; bone marrow suppression) pre-trial screening and close monitoring (including drug levels) will be essential.
Other comments	There will be limited interest from pharmaceutical industry as none of these drugs are licensed for ulcerative colitis.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.4 FRR4 Maintenance treatment for people with mild to moderate ulcerative colitis

Research question:

What is the clinical and cost effectiveness of regular maintenance treatment compared with no regular treatment (but rapid standard treatment if a relapse occurs) in specific populations with mild to moderate ulcerative colitis?

Why this is important:

Maintenance treatment reduces the chance of relapses occurring, but for much of the time a drug is being taken with no obvious benefit, and it may have side effects. An exacerbation of ulcerative colitis can usually be effectively treated or stopped if treatment is given when the first symptoms or signs of a relapse appear. It may be both clinically and cost effective to manage ulcerative colitis in this way, with people receiving episodic treatment rather than taking a drug continuously. This form of treatment may be appropriate if relatively few (for example 1 or 2) mild relapses occur per year. The study population would be people in whom mild to moderate ulcerative colitis of any extent is in remission and who are not taking immunomodulator or biological drugs.

Criteria for selecting high-priority research recommendations:

PICO question	Population – people who have just had amild to moderate exacerbation of ulcerative colitis who are now in remission.

	Intervention – regular maintenance treatment (daily dosing). Comparison – no regular treatment (eg intermittent, tapering down, or no treatment at all). Outcome – critical outcomes would include: clinical relapse (time to relapse); health-related quality of life.
Importance to patients or the population	For patients who have a low risk of relapse, answering this question could potentially reduce unnecessary medication, and its associated side effects and cost, if no maintenance treatment is found to be a clinically and cost effective option for this specific subgroup of patients.
Relevance to NICE guidance	Future NICE guidance may recommend no maintenance treatment for people with mild to moderate ulcerative colitis.
Relevance to the NHS	Potential cost-saving on unnecessary drugs taken continuously for no benefit.
National priorities	If no maintenance treatment is at least as effective in maintaining remission as regular maintenance treatment people would not have to take unnecessary drugs continuously.
Current evidence base	The NICE Ulcerative Colitis Guideline Development Group systematic review found little evidence available to indicate that no maintenance is a clinically effective and cost effective option to maintain remission.
Equality	The research has no equality issues.
Study design	Studies to investigate this would be with patients in whom mild to moderate ulcerative colitis of any extent is in remission and who are not taking immunomodulator or biological drugs.
Feasibility	No issues noted.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.5 FRR5 Risk tool for predicting the likelihood of needing surgery for adults with acute severe ulcerative colitis

Research question:

To develop and validate a risk tool that predicts the likelihood of needing surgery for adults admitted to hospital with acute severe ulcerative colitis.

Why this is important:

Acute severe ulcerative colitis is a life-threatening emergency. About 30% of people admitted to hospital with acute severe ulcerative colitis will require colectomy to avoid colonic perforation during the emergency admission. The Truelove and Witts' severity index is used to define the clinical severity of disease on admission but has not been validated as a predictor of the need for colectomy during treatment. The Travis (Oxford) criteria are used to predict the likelihood of colectomy after 3 days of treatment with intravenous steroids, but may be less useful later in the course. No tools have been developed and validated in patients receiving rescue therapy with anti-tumour necrosis factor (TNF) antibodies or ciclosporin. A validated tool that can reliably predict a person's likelihood of needing a colectomy over the course of an admission to hospital for treating acute severe ulcerative colitis would allow the medical and surgical teams and the person to prepare for colectomy and potentially inform decisions about introducing rescue therapy with ciclosporin or infliximab and when continued medical therapy is unlikely to be successful. There may also be psychological and nutritional benefits to the person and cost benefits to the NHS (for example, shorter length of inpatient stay; decreased risk of infection; less use of rescue therapy). The tool would be developed by a derivation study using a prospective cohort. The tool would be validated using a different prospective cohort from that of the derivation study.

Criteria for selecting high-priority research recommendations:

PICO question	**Derivation study** Population – adults with acute severe ulcerative colitis. Prognostic factors – defined a priori to specify the variables to include in the model on the basis of traditional risk scores and other factors thought to affect the outcome: • risk factors - stool frequency, pyrexia, tachycardia, colonic dilatation, low albumin, low haemoglobin, high platelet count, CRP>45mg/l • other factors, rescue therapy. Outcome – colectomy during hospital admission.
Importance to patients or the population	It would be of great help to patients if they could be advised at different stages of their hospital admission about the chance of requiring surgery or escalation of medical therapy. This would inform the decision as to whether to continue current treatment, escalate medical treatment or proceed to colectomy.
Relevance to NICE guidance	The answer to this question will provide new knowledge and evidence and is very likely to change the management of people admitted to hospital with acute severe ulcerative colitis. The result will add to the NICE guidance.
Relevance to the NHS	There may be cost benefits to the NHS eg shorter length of inpatient stay; decrease risk of infection; less use of "rescue therapy".
National priorities	None.
Current evidence base	The current evidence base is limited by lack of blinding, assessment at different points in each study, variable availability of validation studies and appropriately designed studies have not been undertaken in patients receiving optimised rescue therapy.
Equality	Not applicable.
Study design	Derivation study - a prospective cohort study to develop the tool. Validation study - a different prospective cohort from that of the derivation study to validate the tool.
Feasibility	The proposed research can be carried out in a realistic timescale and at an acceptable cost. There are no specific ethical or technical issues.
Other comments	This study could be run from a single centre – with multi-centre participation. A research fellow would be required to design a database to collate and analyse data. Clinicians could be invited to identify cases and to complete an online database. Similar methodology to audit used to produce Rockall score for patients with acute upper GI bleeding.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.2 Other future research recommendations

1. In children and young people with ulcerative colitis receiving steroid treatment, what are the clinical benefits of routine monitoring of bone density, what tests should be done and how frequently?

2. A registry to collect data to answer 'What are the potential harms or benefits of drug treatments in pregnant women with ulcerative colitis?'.

3. What are the information needs of people with ulcerative colitis when they are considering surgery?

4. What is the clinical and cost effectiveness of sulphasalazine compared to high-dose branded mesalazine for induction of remission for people with mild moderate ulcerative colitis?

5. What is the validity, reliability and accuracy of available adult risk tools as a predictor for the need for surgery in people admitted into hospital with acute severe ulcerative colitis?

6. What is the validity, reliability and accuracy of the paediatric ulcerative colitis activity index (PUCAI) as a predictor for surgery for children and young people admitted to hospital with acute severe colitis?

7. In people with mild to moderate ulcerative colitis, what are the best second-line treatment strategies for induction of remission after people have failed to respond to ASA mono or combination therapies?

8. In people with subacute ulcerative colitis, what are the best second-line treatment strategies for induction of remission after people have failed to respond to oral prednisolone?

9. In people with mild to moderate ulcerative colitis, what are the best strategies for the induction of remission after people have failed to respond to tacrolimus?

10. Establish a national registry to identify the incidence of growth failure and/or pubertal delay in ulcerative colitis and the relationship with treatment (to record treatment [steroids, ASA, immunomodulators] and growth [z scores]).

7 Appendix N: Author definitions

7.1 Remission and improvement definitions

Table 95: Study definitions of remission and improvement for the induction of remission

Study reference	Clinical remission	Endoscopic remission	Clinical and endoscopic remission	Clinical improvement
ANDUS2008/ANDUS2010	DAI<4	≥1 point decrease in DAI from baseline to final visit (LOCF)	EI<4	
ARDIZZONE1999	CAI<4		EI<6	CAI<4, EI<6
BARMEIR2003	DAI≤3 at the end of treatment			
Baron 1962			Clinical and endoscopic remission (no symptoms; inactive or normal mucosa). Patient reported bleeding or mucus in the stool, sense of well being, sigmiodoscopy-grade. According to Lennard-Jones et al (1960)- active, moderately active, inactive or normal.	
BIANCONE2007		Response: a reduction in DAI score of≥1 point		
BINDER1987	Change in disease activity according to the Binder scale (Grade 0).	Change in disease activity according to the Binder scale (Grade 0).		Change in disease activity according to the Binder scale (Grade 0 or 1).
BOSSA2007	Stool frequency < 3/day on day 7 and no visible blood			
CAMPIERI1988	When symptoms (such as motions, blood, mucus) had completely disappeared	A reduction of at least one grade of activity according to the adopted evaluation scale	Repaired rectal mucosa	
CAMPIERI1990	Symptomless, with no more than 2 bowel movements/day without visible	A decrease in the severity of symptoms and signs, not meeting the criteria for	According to Baron's criteria	

	blood	remission, plus those in remission		
CAMPIERI1990A	Complete disappearance of symptoms	A reduction of at least one grade from the baseline value according to the adopted evaluation scale	Rectal mucosa was repaired	
CAMPIERI1991	Symptoms of active disease had resolved	At least one grade of reduction in activity according to the criteria adopted	Rectal mucosa was repaired with the appearance of a vascular pattern	
CAMPIERI1991A	Symptoms of active disease (such as bleeding or mucus) had disappeared	Reduction of at least one grade of activity according to the adopted scale	Repaired rectal mucosa	
CAMPIERI1993	Physician's clinical global evaluation of disease activity. Return to normal stool frequency, no visible blood in the stools, no abdominal symptoms	Decrease in the severity of symptoms not meeting the criteria for remission) – figures include those classed as improved and those in remission	Grade 0, normal mucosa. Modified Baron's criteria	
CAMPIERI2003	DAI score <3			Reduction of at least 3 points in DAI score from baseline
CORTOT2008	$CAI_{1\text{-}4} \leq 2$		Endoscopic score <4 (according to Rachmilewitz)	
CORTOT2008	$CAI_{1\text{-}4} \leq 2$		Endoscopic score <4 (according to Rachmilewitz)	
D'HAENS2010				CAI reduction by at least 50% of the baseline value (Rachmilewitz) or remission (CAI<4)
DANIELSSON1987			Score of 0 on endoscopy (Truelove & Richards)	

DHAENS2001				Improvement in the clinical-activity score. Response was defined as a score of < 10 on days 7 and 8 with a drop in the score from day 1 to day 8 of at least 3 points and the possibility to discharge the patient
DHAENS2006	UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency and at least a 1 point reduction from baseline.			
DICK1964				'Improved or much improved' based on patients wellbeing, decrease in stool frequency, and return to normal consistency, decrease / disappearance in pus, mucus and blood.
FARUP1995	Complete response DAI ≤2.			
FARUP2001	Enhanced UCDAI (includes the PFA) score of 0-1			Enhanced UCDAI reduction of ≥2. This is added to those in remission to give all those that improved.
FERRY1993	Asymptomatic- free from all symptoms, formed bowel movements, no visible blood (all of the above for at least 7 days)	Normal mucosa	Normal mucosa and asymptomatic.	
FRIEDMAN1986A	According to author defined scale (max 6). Clinical score of 1.	According to author defined scale (max 6). Score of 0.		Decrease in clinical score of ≥1
GIBSON2006	CAI≤4	EI<4		Clinical remission or improved CAI≥3 from baseline.
GIONCHETTI1998	DAI=0 on clinical section	DAI=0 on the sigmoidoscopic section		Much improved, PGA score of 1

GREEN1998	Symptom free; If the following variables: consistency, stool frequency, blood on stools, blood on toilet paper, mucus, abdominal pain, need to go to the lavatory and other symptoms interfering with sleep, symptoms interfering with normal daily activities, other relevant symptoms, use of rectal hydrocortisone, were classed as none, absent, normal or no , as appropriate.		Complete remission (symptomatic remission with no use of relief medication in the previous 4 days and grade 0 or 1 UC on sigmoidoscopy)	
GROSS2006	CAI≤4 at the final/ withdrawal visit in the PPA population	Based on the CAI, no further information given	According to Rachmilewitz	
GROSS2011	CAI score ≤4 with a stool frequency <18/week and 0-1blood stool/ week	EI≤3		Complete or marked or slight improvement of symptoms on the Physician's Global Assessment
HANAUER1993	PGA score of 1: complete relief of symptoms	Sigmoidoscopic score of 0-4 out of 15		Treatment benefit (complete relief of symptoms, marked, moderate or slight improvement of symptoms, PGA score of 1, 2, 3 & 4)
HANAUER1996	According to the number of bowel movements and the amount of blood in the stool. This definition was taken from the Cochrane systematic review on oral ASAs.	A 5 point scale where remission was a score of 0 or 1.		
HANAUER1998	Physician's Global Assessment score of 1, complete resolution of symptoms	PGA score of 1 or 2	Score of <4	

HANAUER1998A			Sigmoidoscopic grade 0	≤3 stools/day, no blood, no urgency, no abdominal pain or painful evacuations and a sigmoidoscopic score of 0. This had to be achieved in the preceding 2 days to the visit.
HANAUER2005			Complete remission (complete resolution of stool frequency (normal), rectal bleeding (none), PFA score (generally well), endoscopy (normal) and a PGA score of 0.	Treatment success (complete remission or a clinical response to therapy (improvement in the baseline PGA score and improvement in ≥1 clinical assessment (stool frequency, rectal bleeding, PFA, endoscopy findings) and no worsening in any other clinical assessment.
HANAUER2007			Complete remission (normal stool frequency, no rectal bleeding, a PFA score of 0 (generally healthy), normal endoscopy findings and a PGA score of 0 (quiescent disease activity)	Overall improvement (complete remission or response to therapy.
HARTMANN2010	CAI <4	EI <2 at week 8		
HETZEL1986				A change of at least two grades in symptomatic wellbeing to good or very good by week 6
HIWATASHI2011	0-1 in total score (UCDAI)			Efficacy was defined as a reduction over 2 scores (UCDAI)
ITO2010A	UCDAI≤2 and a bloody stool score of 0 at the final assessment			Patients with a decrease in UCDAI by ≥2 points except patients who experienced a remission. For our analysis the remission figures were combined to give an overall number of those who had

				improved.
JEWELL1974	Not meeting the mild/moderate/severe Truelove and Witts criteria	Normal appearances (score of 0)		
JIANG2004	Defecation 0-2 times/day, no gross blood or microscopic red cells in stool.	Among the 7 items, 5 or more lowered by a grade after treatment	Subsidence of clinical symptoms with relative normal mucous membrane in colonoscopy.	Defecation 3-4 times per day with no gross blood in stool but less than 10 RBC per high power microscopic field.
KAMM2007	Score of 0 points for stool frequency and rectal bleeding (UCDAI)	Modified sigmoidoscopy score of ≤1, with no mucosal friability.	Modified UCDAI≤1 with rectal bleeding and stool frequency of 0, no mucosal friability and ≥1 point reduction in sigmoidoscopy score from baseline.	Decrease of ≥3 points from baseline in the total modified UCDAI score.
KOLKMAN2004	CAI ≤4 or 30% decrease			CAI decrease greater than 30%
KRUIS2003	CAI≤4	EI<4		CAI decreased by at least 3 points.
KRUIS2009	CAI≤4	EI<4		Decrease in CAI by at least 1 point from baseline to the individual study end.
LAMET2011	DAI<3			
LAURITSEN1986	Based on a diary in which the number of bowel movements and presence of absence of blood.		Assessed using Binder 4-point scale, E_0= inactive, C_0= inactive	
LEE1996	≤3 stools per day with no blood.	Grade 1 – normal findings including minor abnormalities in vascular pattern		
LEE1996	≤3 stools per day with no blood.	Grade 1 – normal findings including minor abnormalities in vascular pattern		
LÉMANN1995	No blood (score =0) and little or no mucus (score =0 to	Score =0 on pre-defined 4 point scale.		

	1) judged on 3 point scale.			
LENNARD JONES1960			Remission of the disease is defined as freedom from symptoms combined with the finding of an inactive or, rarely, normal mucosa on sigmoidoscopy.	
LEVINE2002			Normal stool frequency and no blood in stool for 48hrs before visit. PGA score of 'quiescent' and a sigmoidoscopic score of mild or normal.	Improvement by at least one category in the four category disease activity score i.e. normal, mild, moderate, severe
LICHTENSTEIN2007	Scores of 0 for total stool frequency and total rectal bleeding.		Modified UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency, and at least a 1 point reduction in sigmoidoscopy score.	Decrease of ≥3 points from baseline in the overall modified UCDAI.
LICHTIGER1994				A clinical-activity score of less than 10 on two consecutive days
LINDGREN2002				Absence of clinical symptoms (no blood in stools, and <3 bowel movements/24hrs) and an endoscopic score of 0-1
LOFBERG1996		Endoscopic remission (score of 0) after 4 weeks. Normal =0, Granularity, oedema and lack of normal vascular pattern= 1, Hyperemia, friability and petechiae and all of score 1 =2, Ulcerations(and all of score 1 and 2)=3.		

LOFBERG1994			Score of 0 on endoscopy (Truelove & Richards)	Score of 0 on endoscopy and ≤3 stools/day without blood
MARAKHOUSKI2005	CAI≤4			
MARTEAU2005	UCDAI≤1			decrease in UCDAI >2 points
MEYERS1987				Reduction in the global clinical colitis activity that allowed reclassification into a milder category or if there was a lower overall sigmoidoscopic score or both.
MIGLIOLI1990	No more than two bowel movements per day with no visible blood in the stool in the symptom less patient			Clear decrease in severity of symptoms and signs not satisfying remission criteria.
MULDER1988				Decrease of ≥2 according to Van der Heide
OGATA2006	DAI≤2, with no individual score >1	Mucosal healing, score of 0 or 1		Partial and complete response base on DAI >4 points all categories improved).
OGATA2012	DAI score ≤2	Mucosal appearance subscore of 0 or 1)		Clinical response (reduction in DAI of at least 4 points and improvements in all 4 categories; stool frequency, rectal bleeding, mucosal appearance and physician's overall assessment).
OREN1996	Mayo score (including sigmoidoscopy results) of ≤3 with the condition that the patient was not being administered steroids or a score of ≤2 without sigmoidoscopy results			
POKROTNIEKS2000	CAI≤4, associated with a decrease of at least 2 points from baseline	Investigator's global assessment: complete relief, marked or slight	EI≤3	

		improvement (therapeutic benefit)		
POWELLTUCK1978	Remission, activity score =0			A reduction in score by two or more points
POWELLTUCK1986			Non friable rectal mucosa (grade 0)	Non friable rectal mucosa (grade 0) and a score of -0 for all clinical variables (malaise, bowel frequency, stool consistency, rectal bleeding)
PRANTERA2005	CAI≤4, according to Rachmilewitz	EI≤2		
PRUITT2002	PFA score of normal or mild and absence of rectal bleeding.		Symptomatic remission plus a sigmoidoscopic evaluation score of normal or mild.	
RAEDLER2004	CAI_{1-4}≤2	EI≤2	CAI_{1-7}≤4 and EI≤2	
RIJK1991			No definition was given, but the Cochrane systematic review included it as an 'author defined outcome' – assessment based on clinical and endoscopic criteria.	
RIZELLO2002	DAI score <3	Based on Baron's criteria		Reduction of at least 3 points in DAI score from baseline
RIZZELLO2003				Disease activity Index -> reduced by at least 1 point from baseline
ROBINSON1988				Unknown definition- The inclusion criteria for the Cochrane Systematic review was 'author defined' definition'
ROMANO2010	Score <10 on PUCAI score	Baron score 0-1		
SANDBORN2009A	Stool frequency score of 0 and rectal bleeding score of 0.		Complete response (PGA score of 0, i.e. complete resolution of or normalization of stool frequency,	Treatment success/overall improvement (partial response: improvement from baseline in the PGA score and no

			bleeding and sigmoidoscopy with CFT assessment score)	worsening in any of the 3 component scores) and complete response (those that have improved or gone into remission)
SANDBORN2012B	Score of 0 for both rectal bleeding and stool frequency subscores from the UCDAI		UCDAI score≤1, with subscores of 0 for both rectal bleeding and stool frequency (based on the 3 days closest to the week 8 visit with no missing diary data within a 5 day window closest to the visit [the 5 days did not include any days on which a colonoscopy or the preparation for colonoscopy occurred]), no mucosal friability on colonoscopy and a ≥1 point reduction from baseline in the endoscopic index score.	≥3 point reduction in the UCDAI score.
SCHERL2009	Score of 0 for rectal bleeding and a combined score of ≤2 for bowel frequency and physician's assessment using the MMDAI subscales at week 8	Mucosal healing (sigmoidoscopy score of 0 or 1)	Complete remission (MMDAI score of ≤1)	
SCHROEDER1987	Complete response (complete resolution of all symptoms, all assessment scores 0 (stool frequency, rectal bleeding and PGA)			Partial response (substantial but incomplete improvement in the assessment scores). The value has been added to those in remission to give the total number of patients who improved.
SELBY1985				Improvement in the clinical factors measured was judged

				to represent a positive response
SNINSKY1991	Complete resolution of symptoms, with all assessment scores determined to be 0.			A reduction in the PGA score and in at least one other component score with no score increased in severity.
SOOD2002	<150 (activity index ,Seo 1992)			
TARPILA1994			Score of 0 or 1 after 4 weeks	
TRUELOVE1995	Indicted by all of 1 or 2 stools a day without blood, no fever, no tachycardia, Hb normal,ESR normal or returning to normal, gaining weight.			Improved but not reached remission
VAN2003				A score of less than 10 on day 8 with a drop of ≥ 3 as compared with baseline
VECCHI2001	CAI<4	EI <4		Reduction in CAI of 50% from baseline
WILLIAMS1987				DAI score of 0
ZINBERG1990				Unknown definition- The inclusion criteria for the Cochrane Systematic review was 'author defined' definition'

7.2 Relapse definitions

Table 96: Study definitions of relapse for the maintenance of remission

Study reference	Remission	Relapse
ANDREOLI1987	Unknown. Included in the Cochrane systematic review.	The development of a new acute phase within 12 months from the beginning of the survey was considered a negative result
ANDREOLI1994	Clinical remission achieved and microscopic inflammation cleared from biopsy specimens	Endoscopic grade >0
ARDIZZONE1999C	Absence of active disease symptoms and no signs of active inflammation on sigmoidoscopy	Increased stool frequency with blood or mucus and evidence of active disease on sigmoidoscopy

AZADKHAN1980	Absence of colitis symptoms and the absence of signs of inflammation on sigmoidoscopy and on histological examination of rectal biopsy specimens as defined by Truelove & Richards	Most relapses were associated with clinical symptoms of colitis but some patients remained free from symptoms but with inflammation on sigmoidoscopy and histology
BARDAZZI1994	Mild symptoms and normal mucosa (endoscopically)	Erythematous and friable mucosa even in the absence of symptoms
COURTNEY1992	Absence of symptoms or the presence of only mild stable symptoms of colitis	Development of new symptoms of colitis sufficiently severe to warrant the introduction of systemic steroid therapy (by an investigator unaware of study treatment)
DALBASIO 1998	**Clinical:** absence of visible blood in the stools and no more than 2 bowel movements per day. **Endoscopic:** Score of 0 (Baron's criteria).	Development of symptoms together with evidence of endoscopic activity (grade >1 of Baron's classification)
DALBASIO1990	Mild symptoms and normal mucosa	Erythematous and friable mucosa, even in the absence of symptoms
DALBASIO1997	Mild symptoms and normal endoscopic appearance of the mucosa.	Presence erythematous and friable mucosa even in the absence of symptoms.
DARIENZO1990	**Clinical:** Absence of blood in the stools and absence of diarrhoea, abdominal pain and tenesmus. **Endoscopic:** Grade 0 or 1.	Identified by clinical activity endoscopically (grade2-4) and histologically (grade2 or3) confirmed, or in the absence of clinical manifestations, by endoscopic and histological evidence of activity.
DHAENS2012	Endoscopic remission withno or mild symptoms	Withdrawal due to lack of efficacy
DIGNASS2009	UCDAI score <2 at enrolment	UCDAI score of 3-8 is a mild/moderate relapse and >8 is severe
DISSANAYAKE1973	Symptom free and normal mucosa on sigmoidoscopy with no significant inflammation on rectal biopsy	Patient reports colitis symptoms and there is definite evidence of inflammation
GREEN1992	Not specified. Clinical and sigmoidoscopic remission.	Symptomatic (7 days of increased stool frequency with or without blood and mucus), sigmoidoscopic (friable mucosa or spontaneous haemorrhage) and histological grounds (active disease) to distinguish it from non inflammatory diarrhoea
GREEN1998A	Asymptomatic (none or only mild symptoms) and had a sigmoidoscopic grade of 0 or 1 (verified by sigmoidoscopy or colonoscopy no more than 3 days before initiation of the study therapy)	**Symptomatic relapse:** Recurrence of moderate or severe symptoms on the patients' overall evaluation. **Asymptomatic relapse:** Grade 3 or 4 on sigmoidoscopy in the absence of symptoms
HANAUER1996A	Endoscopic appearance of the bowel (score of 0) and by the passage of five or fewer bloodless stools/day	Score of ≥1 on endoscopy at any time (score was from 0-3)

HAWKEY1997	Normal sigmoidoscopic appearances with no rectal bleeding during the week before entry and stools that were not liquid	Sigmoidoscopic score of ≥1 or experienced 3 consecutive days of rectal bleeding caused by UC or liquid stools for 1 week
HAWTHORNE1992	Absence of symptoms of active disease in patients not taking corticosteroids and with a sigmoidoscopic appearance of grade 0 or 1 (Baron et al.).	Worsening symptoms recognised by the patient as active disease (such as rectal bleeding, loose motions, or bowel frequency) with a sigmoidoscopic appearance of grade 1 or above or grade 2 or 3 appearance at routine sigmoidoscopy regardless of symptoms.
HAWTHORNE2012		Symptoms of active disease (bloody diarrhoea or rectal bleeding for 3 days or more). With a sigmoidoscopic appearance of grade 2 or 3 using the modified Baron score. If patients were inadvertently treated for active disease – they were classed as relapsers.
IRELAND1988	Absence of colitis symptoms together with an absence of inflammation on sigmoidoscopy	Increased stool frequency with or without blood or mucus and with evidence of inflammation on sigmoidoscopy
ITO2010B		Bloody stool score of 1 or more and UCDAI of 3 or more.
JEWELL1974	Defined by severity of disease using the criteria of Truelove and Witts (1995)	Occurrence of diarrhoea with blood in the motion and with sigmoidoscopic evidence of inflammation
KAMM2008	Clinical and endoscopic remission (UCDAI score≤1), with rectal bleeding and stool frequency scores of 0, a combined PGA and sigmoidoscopy score of ≤1, no mucosal friability and an additional requirement for a ≥1 point reduction from baseline in sigmoidoscopy score (from first part of the trial)	A requirement for alternative treatment for UC, including surgery or an increase in the dose of MEZAVANT XL mesalazine above 2.4g/day.
KANE2003	Absence of blood in the stools, urgency or cramping	>3 on the Harvey-Bradshaw index
KANE2008	Absence of blood in the stools, urgency or cramping. UCDAI score <3	UCDAI score >3 or an increase of more than 3 points during the preceding time interval
KIILERICH1992	No visible blood in the stools for >3 days within the last week and/or <3 stools/day for ≥4 days of the last week and sigmoidoscopy grade 1-2 at admission (no spontaneous bleeding without or with distinct vessels in the mucosa)	Inflammation of the rectal mucosa grade 3-4 on sigmoidoscopy (no distinct vessels in the mucosa, spontaneous bleeding and bleeding by contact with the sigmoidoscope)
KRUIS1995	Required normal endoscopic grading	Patients with a change in their normal endoscopic grading to at least moderate activity

KRUIS2001	**Clinical remission:** CAI<6. **Endoscopic remission:** CI<4. Remission of UC was both clinical and endoscopic remission	Both clinical and endoscopic relapse: CAI≥6 and EI>4 at completion of the study.
KRUIS2011	CAI≤4 and EI≤3	CAI>4 and an increase of ≥3 from baseline
MANTZARIS1994	Full clinical, endoscopic and histological remission (indexes not described)	Erythema and loss of vascular pattern were found at endoscopy and if the histology of biopsy specimens taken from these areas showed the presence of acute and chronic inflammatory cell infiltrate.
MANTZARIS2004	Absence of symptoms of colitis in view of a normal sigmoidoscopy with biopsies (UCDAI 0-1).	Development of new symptoms sufficiently severe to warrant treatment with steroids in view of an abnormal sigmoidoscopy (UCDAI>3)
MARTEAU1998	**Clinical remission:** No rectal bleeding, no mucus in the stools, no diarrhoea, no pain, and no tenesmus	Occurrence of clinical symptoms with an increase in the endoscopy score ≥1 when compared with the endoscopy score at entry, or occurrence of rectal bleeding > twice a day.
MATEJIMENEZ2000	Mayo Clinic score <7	Mayo Clinic score of ≥7
MINER1995	Sigmoidoscopic index of <5, mean of <5 stools per day, absence of rectal bleeding	Three definitions: 1. Sigmoidoscopic index of ≥5 and ≥1 of the following: mean of ≥5 trips to the toilet for 3 of 7 continuous days or the presence of rectal bleeding for 3 of 7 continuous days. 2. Sigmoidoscopic index of ≥5 with missing data for trips to the toilet or rectal bleeding at the end of the study/final visit 3. Missing data for the final Sigmoidoscopic index and early termination from the trial due to insufficient therapeutic effect
MISIEWICZ1965	Absence of symptoms. If the patient remained symptom free, the finding of a haemorrhagic mucosa on sigmoidoscopy did not constitute a relapse.	Recurrence of symptoms.
NILSSON1995	Grade 1 or 2 on endoscopy and no symptoms indicating relapse, such as diarrhoea or rectal bleeding	Suspected if there are >3 stools/day for >5 days and/or visible blood in stool for >4 consecutive days. Confirmed by endoscopy – macroscopic changes of grade 3 or 4 in the rectum.
OREN1996	Mayo score (including sigmoidoscopy results) of ≤3 with the condition that the patient was not being administered steroids or a score of ≤2 without sigmoidoscopy results	≥3 points in Mayo Clinic score (not including sigmoidoscopy) and/or reintroduction of steroids at a dose of ≥300mg/month
PAOLUZI2005	Absence of symptoms and endoscopic /histological changes typical of active UC	As per the Truelove & Witts criteria.

PRANTERA2009	Score of ≤1 on the UC disease activity index, supported by a rectal sigmoidoscopy in the preceding 3 months or colonoscopy in the preceding 6 months.	UCDAI score >1
RIIS1973	Free from symptoms	If rectal bleeding occurred for >3 successive days or the patients had had ≥3 defecations daily for >5 successive day.
RIJK1992	Absence of clinical signs of inflammation i.e. 3 stools or less per day without blood and a normal mucus membrane on sigmoidoscopy	Blood in stools, with or without diarrhoea and signs of inflammation on endoscopy. Also if at 48 weeks there was endoscopic inflammation but no presence of complaints.
RILEY1988A	Absence of blood in the stool	Symptomatic deterioration resulting in a sigmoidoscopy which confirms the macroscopic grading to be worse
SANDBERGGERTZEN1986	<4 bowel movements per day without visible blood or mucus and with no signs of active disease at sigmoidoscopy	Occurrence of diarrhoea with macroscopic blood together with the finding of active inflammation on sigmoidoscopy.
SANDBORN2010	Simple Clinical Colitis Activity Index (SCCAI) score of ≤2	Simple Clinical Colitis Activity Index score of ≥5
SOOD2000	**Complete remission:** Clinical improvement with absence of symptoms of active disease (rectal bleeding, bowel frequency) with sigmoidoscopic appearance of grade 0-1 and normal histological pattern. **Partial remission:** Clinical improvement with stool frequency still increased but less than 50% of previous and sigmoidoscopy showing downgrading of severity and granular non friable mucosa (grade 0-22)	Remission followed by worsening of symptoms recognized by the patient as active disease (such as rectal bleeding, loose motions or bowel frequency) with sigmoidoscopic appearance of active colitis.
SOOD2002A	Clinical improvement with the absence of symptoms of active disease (rectal bleeding, bowel frequency) with the sigmoidoscopic appearance of grade 0-1 and a normal histological pattern. It was also defined as a score of 150 or lower on the ulcerative colitis disease activity index.	Remission followed by worsening of symptoms, recognized by the patient as active disease (such as loose stools/ bowel frequency or rectal bleeding) wit the sigmoidoscopic appearance of active colitis.

SOOD2003	Clinical improvement with absence of symptoms of active disease (rectal bleeding, bowel frequency) with sigmoidoscopic appearance of grade 0 and normal histological findings, or as a score of 150 or lower on the ulcerative colitis disease activity index.	Worsening of symptoms (bowel bleeding, increased frequency, loose stools) with sigmoidoscopic evidence of active colitis (granularity, friability, spontaneous bleeding).
TRAVIS1994	No clinical symptoms of active disease and no signs of active inflammation on sigmoidoscopy (grade0: normal, 1: pink mucosa of quiescent colitis without visible vessels)	Increase in bowel frequency with blood or mucus and evidence of active disease on sigmoidoscopy
WRIGHT1993	Inactive UC diagnosed by the Truelove & Witts criteria	Relapse of diarrhoea (with or without blood and mucus) thought by the attending physician to warrant introduction of rectal or oral corticosteroids.
YOKOYAMA2007	Absence of symptoms and a score of <4 on the CAI.	Score of 6 or higher on the CAI and >3 in the endoscopic index (EI). Even if the CAI score was lower than 6, the additional use of any medicine was considered a relapse since corticosteroids, antibiotic drugs, immunosuppressive agents, antidiarrhoeal agents and also 5-ASA enemas more than twice a week could influence the activity of UC. Patients in whom the dose of corticosteroids could not be decreased were also considered as having relapsed.

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