National Institute for Health and Care Excellence

Final

Diverticular disease: diagnosis and management

[P] Evidence review for management of recurrent acute diverticulitis

NICE guideline NG147

Intervention evidence review

November 2019

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the most clinically and cost effective management strategy for people with recurrent episodes of acute diverticulitis?

1.2 Introduction

Episodes of acute diverticulitis typically impose a significant burden on patients in terms of symptoms, disability and mortality as well as the significant costs associated with inpatient assessment and treatment. The complications of interventions, such as post-operative pain and adhesions following surgery, typically result in additional symptoms and impaired quality of life for patients. The development of sepsis, a serious potential consequence of an episode of acute diverticulitis, may limit longevity and quality of life in the long term, even when recovery is achieved through successful treatment. Strategies which achieve reductions in the adverse effects of acute diverticulitis for patients who experience recurrent episodes could bring significant clinical and cost benefits.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over with recurrent acute diverticulitis/in remission from a previous episode of acute diverticulitis at risk of recurrent diverticulitis
Interventions	• Aminosalicylates • Surgery • Conservative measures - weight loss, exercise, dietary advice • Laxatives • Antibiotics • Probiotics
Comparisons	• Each other • Placebo • No intervention

Outcomes	Critical outcomes:
	• Quality of life
	• Mortality
	• Complications
	  ○ infections
	  ○ abscesses
	  ○ perforation
	  ○ fistula
	  ○ stricture
	• Recurrence rates of acute diverticulitis
	• Hospitalisation related to diverticular disease
	• Need for surgery for diverticular disease

	Important outcomes: • Symptom control: pain relief, bloating, night sweats, fever • Side effects of: ○ antibiotics, nausea and vomiting, antibiotics-related infection ○ analgesics, constipation , nausea and vomiting ○ surgery, morbidity and mortality
Study design	RCTs If not enough RCT evidence, consider observational studies

1.4 Clinical evidence

1.4.1 Included studies

Five studies were included in the review;[24, 26, 29, 33, 40] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix H.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Kruis 2017[24]	**Aminosalicylate (3g/d):** Mesalamine 3g once daily n=263 **Aminosalicylate (1.5g/d):** Mesalamine 1.5g once daily n=125 **Placebo:** placebo n=287	Adults who had a prior diagnosis of left-sided uncomplicated acute diverticulitis confirmed by ultrasonography or computed tomography (CT) within the preceding 6 months and has been brought to clinical remission. Age: < 60 years: 122 > 60 years: 89 Germany	• Recurrent diverticulitis Follow up at 48 weeks	
Lanas 2013[26]	**Antibiotic + dietary fibre:** 2 tablets of rifaximin polymorph alpha b.d. (total 800 mg per day) for the first week of each 4 week period + 3.5g b.d. of plantago ovata husk (dietary fibre) taken daily for 48 weeks. n=77 **Dietary fibre only:** 3.5g b.d. of plantago ovata husk (dietary fibre) taken daily for 48 weeks. n=88	Adult patients aged ≥18 years with one or more recent (within the previous two months) episodes of acute diverticulitis but in remission at the time of enrolment. Recent episodes confirmed by CT scan, ultrasonography or endoscopy. Mean age: 54.1±12.5	• Recurrent diverticulitis • Hospitalisation • Symptoms (intensity) Follow up at 48 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
		Spain		
Parente 2013[29]	**Aminosalicylate:** Mesalazine (Pentacol®) 800 mg one tablet b.d. for 10 days every month n=45 **Placebo:** Identically appearing placebo one tablet b.d. for 10 days every month n=47	Adults with documented episode of uncomplicated diverticulitis during the last months (maximum 12 months), recruitment which was considered possible only after the complete clinical remission of diverticulitis flare. Mean age: 61.5 Italy	• Recurrent diverticulitis Follow up at 2 years	
Raskin 2014[33]	**Aminosalicylate (4.8g/d):** Mesalamine 4.8g daily (four 1.2-g tablets) n=299 **Aminosalicylate (2.4g/d):** Mesalamine 2.4g daily (two 1.2-g tablets plus two placebo tablets) n=290 **Aminosalicylate (1.2g/d):** Mesalamine 1.2g daily (one 1.2-g tablets plus three placebo tablets) n=291 **Placebo:** Four placebo tablets daily n=289	Adults with ≥1 documented episodes of acute diverticulitis in the previous 24 months that resolved without colonic resection, and without signs or symptoms of diverticulitis within 6 weeks of enrolment. Mean age: 55.7±11 USA	• Recurrent diverticulitis • Surgery • Quality of life Follow up at 2 years	

Study	Intervention and comparison	Population	Outcomes	Comments
Tursi 2007[40]	**Aminosalicylate + probiotic:** Balsalazide 2.25g for 10 days/month plus VSL#3 450 billions/day for 15 days every month. n=15 **Probiotic:** VSL#3 450 billions/day for 15 days every month. n=15	Patients affected by uncomplicated acute diverticulitis, confirmed by colonoscopy. Mean age: 60.1 (47-75) Italy	• Recurrent diverticulitis • Symptom: abdominal pain Follow up at 1 year	All patients received balsalazide 2.25 g daily plus rifaximin 800 mg/day for the first 10 days to achieve remission

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Evidence not suitable for GRADE analysis

Study	Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
Raskin 2014[33]	Aminosalicylate (4.8g/d)	Quality of life (EQ-5D)	NA	268	-	-	High
	Aminosalicylate (2.4g/d)		NA	261	-	-	
	Aminosalicylate (1.2g/d)		NA	265	-	-	
	Placebo		NA	257	-	-	

Study	Comparison	Outcome	Intervention results	Intervention group (n)	Comparison results	Comparison group (n)	Risk of bias
			Overall, the EQ-5D result revealed no patterns or trends across study arms at baseline or week 104.				
Tursi 2007[40]	Aminosalicylate + probiotic vs probiotic	Symptom score: abdominal pain	NA	15	NA	15	High
			Abdominal pain scores at the end of follow-up were statistically significantly lower in balsalazide/VSL#3 group than in VSL#3 alone group.				

Table 4: Clinical evidence summary: Aminosalicylate (4.8g/d) compared to aminosalicylate (2.4g/d) recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate (2.4g/d)	Risk difference with Aminosalicylate (4.8g/d) (95% CI)
Recurrent diverticulitis	529 (1 study) 2 years	LOW[1] due to imprecision	RR 0.97 (0.75 to 1.26)	Moderate	
				307 per 1000	9 fewer per 1000 (from 77 fewer to 80 more)
Surgery	529 (1 study) 2 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.22 (0.33 to 4.48)	Moderate	
				15 per 1000	3 more per 1000 (from 10 fewer to 52 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 5: Clinical evidence summary: Aminosalicylate (4.8g/d) compared to aminosalicylate (1.2g/d) recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate (1.2g/d)	Risk difference with Aminosalicylate (4.8g/d) (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate (1.2g/d)	Risk difference with Aminosalicylate (4.8g/d) (95% CI)
Recurrent diverticulitis	533 (1 study) 2 years	⊕⊕⊖⊖ LOW1 due to imprecision	RR 1.03 (0.79 to 1.34)	Moderate	
				291 per 1000	9 more per 1000 (from 61 fewer to 99 more)
Surgery	533 (1 study) 2 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.82 (0.25 to 2.67)	Moderate	
				23 per 1000	4 fewer per 1000 (from 17 fewer to 38 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 6: Clinical evidence summary: Aminosalicylate (3g/d) compared to aminosalicylate (1.5g/d) recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Aminosalicylate (1.5g/d)	Risk difference with Aminosalicylate (3g/d) (95% CI)
Recurrent diverticulitis	853 (2 studies) 1-2 years	⊕⊖⊖⊖ VERY LOW1,2 due to inconsistency, imprecision	RR 0.88 (0.73 to 1.37)	Moderate	
				415 per 1000	50 fewer per 1000 (from 112 fewer to 154 more)
Surgery	526 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW2,3 due to risk of bias, imprecision	RR 0.68 (0.19 to 2.37)	Moderate	
				23 per 1000	7 fewer per 1000 (from 19 fewer to 32 more)

1 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p<0.04, unexplained by subgroup analysis.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 7: Clinical evidence summary: Aminosalicylate (4.8g/d) compared to placebo recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (4.8g/d) (95% CI)
Recurrent diverticulitis	525 (1 study) 2 years	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 1.22 (0.92 to 1.61)	Moderate	
				245 per 1000	54 more per 1000 (from 20 fewer to 149 more)
Surgery	525 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 2.4 (0.47 to 12.25)	Moderate	
				8 per 1000	11 more per 1000 (from 4 fewer to 90 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 8: Clinical evidence summary: Aminosalicylate (3g/d) compared to placebo recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (3g/d) (95% CI)
Recurrent diverticulitis	1007 (2 studies) 1-2 years	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 1.22 (1.01 to 1.47)	Moderate	
				277 per 1000	61 more per 1000 (from 3 more to 130 more)
Surgery	518 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.97 (0.36 to 10.66)	Moderate	
				8 per 1000	8 more per 1000 (from 5 fewer to 77 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (3g/d) (95% CI)
at very high risk of bias.					

Table 9: Clinical evidence summary: Aminosalicylate (1.5g/d) compared to placebo recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (1.5g/d) (95% CI)
Recurrent diverticulitis	858 (2 studies) 1-2 years	⊕⊕⊖⊖ LOW1,2 due to inconsistency, imprecision	RR 1.4 (1.15 to 1.71)	Moderate	
				277 per 1000	111 more per 1000 (from 42 more to 197 more)
Surgery	522 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW2,3 due to risk of bias, imprecision	RR 2.91 (0.59 to 14.28)	Moderate	
				8 per 1000	15 more per 1000 (from 3 fewer to 106 more)

1 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p<0.04, unexplained by subgroup analysis.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 10: Clinical evidence summary: Aminosalicylate (cyclic) compared to placebo recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (cyclic) (95% CI)
Recurrent diverticulitis	92 (1 study)	⊕⊕⊖⊖ LOW1,2	RR 0.48 (0.2 to 1.16)	Moderate	
				277 per 1000	144 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Aminosalicylate (cyclic) (95% CI)
	2 years	due to risk of bias, imprecision			(from 222 fewer to 44 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 11: Clinical evidence summary: Aminosalicylate + probiotic compared to probiotic for recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Probiotic	Risk difference with Aminosalicylate + probiotic (95% CI)
Recurrent diverticulitis	30 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.5 (0.05 to 4.94)	Moderate	
				133 per 1000	67 fewer per 1000 (from 126 fewer to 524 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 12: Clinical evidence summary: Antibiotic + fibre compared to fibre for recurrent diverticulitis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fibre	Risk difference with Antibiotic + fibre (95% CI)
Recurrent diverticulitis	165 (1 study)	⨁⨁⊖⊖ LOW1,2	RR 0.54 (0.25 to	Moderate	
				193 per 1000	89 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fibre	Risk difference with Antibiotic + fibre (95% CI)
	1 years	due to risk of bias, imprecision	1.18)		(from 145 fewer to 35 more)
Hospitalisation	165 (1 study) 1 years	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.38 (0.08 to 1.83)	Moderate	
				68 per 1000	42 fewer per 1000 (from 63 fewer to 56 more)
Symptoms (intensity) Scale from: 0 to 10.	165 (1 study) 1 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean symptoms (intensity) in the control groups was 3.26	The mean symptoms (intensity) in the intervention groups was 0.19 higher (1.79 lower to 2.17 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

One study relating to this review question was identified but was excluded as it was assessed as not applicable. [3] This is listed in Appendix H: with reasons for exclusion given. See also the study selection flow chart in Appendix G:.

1.5.3 Unit costs

The following unit costs were presented to the committee.

Table 13: UK costs of laxatives, antibiotics, aminosalicylates and probiotics and prebiotics

Drug	Assumed daily dose [BNF][(a)]	Cost per unit (£)	Cost per month (£)[(b)]	Source
Laxatives				
Isphagula husk 3.5g effervescent granules sachets	2 x 3.5g sachets [5-10g once daily]	£0.09	£5.52	NHS Drug Tariff
Methylcellulose 500mg	2 x 500mg tablets daily [3-6 x 500mg tablets twice daily]	£0.05	£2.89	NHS Drug Tariff
Sterculia 62% granules 7g sachets	2 x 7g sachets twice daily [1-2 sachets 1-2 times a day]	£0.11	£13.53	NHS Drug Tariff
Bisacodyl 5mg gastro-resistant tablets	2 x5mg tablets [5-10mg once daily increased if necessary up to 20mg once daily]	£0.21	£12.66	NHS Drug Tariff
Sodium picosulfate 5mg/5ml oral solution	2 x 5mg/ml solutions [5-10mg once daily]	£0.12	£7.20	NHS Drug Tariff
Senna 7.5mg tablets	2 x 7.5mg tablets [7.5-15mg daily (maximum dose 30 mg daily)]	£0.03	£1.67	NHS Drug Tariff
Lactulose 3.1g-3.7g/5ml oral solution	6 x 3.1g-3.7g/5ml oral solution [Initially 15ml twice daily, adjusted according to response]	£0.02	£4.13	NHS Drug Tariff
Macrogol 3350 oral powder 8.5g sachets	2 sachets [2 sachets once daily usually for up to 2 weeks]	£0.14	£3.89[(c)]	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Docusate sodium 100mg capsules (by mouth)	5 x 100mg capsules [Up to 500mg daily in divided doses, adjusted according to response]	£0.07	£10.60	NHS Drug Tariff
Glycerol (by rectum) 4g suppositories	1 x 4g suppository [4g, as required]	£0.10	£2.94	NHS Drug Tariff
Micralax (sodium citrate 90mg/ml) 5ml micro-enema	1 enema [1 enema per dose]	£0.41	£12.35	British National Formulary
Arachis oil 130ml enema	1 x 130ml enema [130ml, as required]	£47.50	£95[d]	NHS Drug Tariff
Antibiotics (Intravenous)				
Co-Amoxiclav 1000mg/200mg powder for solution for injection	1000mg/ 200mg every 8 hours by intravenous infusion	£1.06	£6.36[d] - £31.80[e]	BNF NHS Indicative price
Ciprofloxacin 400mg/200ml solution for infusion bottles	2x 400mg daily by intravenous infusion	£2.08	£29.12[f]	BNF NHS Indicative price
Metronidazole500mg/100ml infusion 100ml bags	3 x 500mg daily by intravenous infusion	£3.19	£66.99[f]	BNF NHS Indicative price
Ertapenem sodium 1g powder for solution for infusion vials	1g daily by intravenous infusion	£31.86	£127.44[g]- £223.02[f]	BNF NHS Indicative Price
Piperacillin 2g/ Tazobactam 250mg powder for solution for injection vials	4.5g every 8 hours by intravenous infusion	£7.65	£321.30[f]	NHS Drug Tariff
Cefuroxime 750mg powder for solution for injection vials	1.5g every 8 hours; by intravenous infusion [750mg every 6-8 hours; increased if necessary up to 1.5g every 6-8 hours]	£2.52	£45.36[h]	BNF NHS Indicative Price
Amoxicillin 500mg powder for solution for injection vials	3x 500mg daily by intravenous infusion	£0.55	£11.51[f]	NHS Drug Tariff
Gentamicin 240mg/80ml infusion bags	5-7mg/kg daily	£6.13	£85.80[f]	NHS Drug Tariff
Antibiotics (Oral)				
Rifaximin 200mg tablets	4 x 200mg tablets [200mg every 8 hours for 3 days]	£1.68	£47.13[g]	NHS Drug Tariff
Co-Amoxiclav 500mg/125mg tablets	3 x 500mg/125mg tablets daily	£0.08	£2.36[e]	NHS Drug Tariff
Ciprofloxacin 500 mg tablets	2x 500mg tablets daily	£0.08	£1.15[f]	NHS Drug Tariff
Metronidazole 400mg tablets	3 x 400mg daily	£0.25	£5.18[f]	NHS Drug Tariff

Drug	Assumed daily dose [BNF][a]	Cost per unit (£)	Cost per month (£)[b]	Source
Cefadroxil 500mg capsules	2 x 1g capsules daily	£0.32	£9.03[f]	NHS Drug Tariff
Cefuroxime 125mg tablets	4 x 125mg tablets daily	£0.33	£3.91[h]	NHS Drug Tariff
Cefalexin 500mg tablets	500mg every 8 hours	£0.08	£1.71[f]	NHS Drug Tariff
Trimethoprim 200mg tablets	2x 200mg daily	£0.07	£0.93[f]	NHS Drug Tariff
Aminosalicylates				
Mesalazine (Octasa®) 800mg gastro-resistant tablets	2 x 800mg tablets daily for 10 days per month – 6 x 800mg daily [2.4-4.8g daily]	£0.45	£8.97[e] - £81.93	NHS Drug Tariff
Balsalazide sodium 750mg capsules	3 x 750mg capsules [2.25g 3 times daily until remission, then 1.5g twice daily (maximum 6g per day)]	£0.23	£7.02[e]	NHS Drug Tariff
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets	1 x 4.4g sachet daily	£1.15	£17.18[i]	BNF (NHS indicative price)

(a) Dosages for adults, British National Formulary
(b) Depending on number of units taken
(c) Cost per 14 day course; not per month
(d) Cost when dose taken for 2 days
(e) Cost when dose taken for 10 days
(f) Cost when dose taken for 7 days
(g) Cost when dose taken for 4 days
(h) Cost when dose taken for 3 days
(i) Cost when dose taken for 15 days

Table 14: UK costs to people with diverticular disease for items not prescribed on the NHS

Drug	Assumed daily dose[a]	Cost per unit (£)	Cost per month (£)[b]	Source
Dietary Fibre				
Glucomannan 500mg capsules	4 x 500mg capsules-8 x 500mg capsules	£0.12	£14.18-£28.37	Not available in BNF; Retail price from stockist[d]
GG Scandinavian Bran Crispbread (4.26g dietary fibre)	6 crispbreads (4.26g dietary fibre per crispbread)	£0.13	£24.20	Not available in BNF; Retail price from stockist[d]
Probiotics and prebiotics				
VSL#3 Probiotic food supplement oral powder 4.4g sachets (non-prescribed)	1 x 4.4g sachet daily	£2.35	£71.47	Retail price from stockist[e]
Vivomixx (450 billion live bacteria per	1 x 4.4g sachet daily	£1.48	£45.02	Retail price from stockist[e]

Drug	Assumed daily dose[a]	Cost per unit (£)	Cost per month (£)[b]	Source
sachet) 4.4g sachets				
Lactobacillus casei: Probio 10 (containing *L. casei* 5x10^7 viable cells, among 10 different species of micro-organisms)	1 capsule daily	£0.08	£2.53	Not available in BNF; Retail price from stockist[d]
Symprove™	1ml/kg	£0.03/ml	£75.14[c]	Not available in BNF; Retail price from stockist[f]

Sources: Amazon.co.uk, Holland and Barrett, shop.symprove.com
(a) Dosages for adults
(b) Depending on number of units taken
(c) Cost exclusive of VAT for a weight of 75kg calculated from the average BMI (BMI 27.7) reported in Kvasnovsky 2017[25]
(d) Retail price obtained from Holland and Barrett
(e) Retail price obtained from Amazon.co.uk
(f) Retail price obtained from shop.symprove.com

1.6 Evidence statements

1.6.1 Clinical evidence statements

Comparison between aminosalicylate doses

No clinically important difference was seen when comparing 4.8g/d of aminosalicylate to either 2.4g/d (n=529, low to very low quality) or 1.2g/d (n=533, low to very low quality) aminosalicylate in one study for recurrent diverticulitis and surgery outcomes. Similarly there was no clinically important difference seen when comparing 3g/d to 1.5g/d aminosalicylates for either recurrent diverticulitis (2 studies, n=853, very low quality) or surgery (1 study, n=526, very low quality).

Aminosalicylate vs placebo

No clinically important benefit was seen when comparing 4.8g/d of aminosalicylate to placebo for recurrent diverticulitis and surgery outcomes in one study (n=525, moderate to very low quality). There was also no clinically important difference seen when comparing 3g/d aminosalicylate to placebo for recurrent diverticulitis (2 studies, n=1007, moderate quality) and surgery (1 study, n=518, very low quality).

Evidence of low quality demonstrating a clinically important benefit of cyclic aminosalicylate (1 study, n=92) was seen when compared to placebo for recurrent diverticulitis. However, low quality evidence demonstrated a clinically important harm of 1.5g/d aminosalicylate (2 studies, n=858) when compared to placebo for recurrent diverticulitis.

Aminosalicylate plus probiotic vs probiotic alone

One small study with very low quality evidence demonstrated no clinically important difference between aminosalicylate plus probiotic and probiotic alone for recurrent diverticulitis (n=30).

Antibiotic plus fibre vs fibre alone

One study demonstrated no clinically important difference between antibiotic plus probiotic and probiotic alone for recurrent diverticulitis, hospitalisation and symptoms outcomes (n=165, low to very low quality).

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee identified quality of life, mortality, recurrence of diverticulitis, hospitalisation, surgery or complications (infections, abscesses, perforation, stricture and fistula) as the critical outcomes. The following outcomes were identified as important for management of recurrent diverticulitis; symptom control, and side effects of the interventions. No evidence was identified for the interventions of surgery, laxatives or conservative measures of weight loss or exercise.

1.7.1.2 The quality of the evidence

The quality of evidence ranged from very low to high. The majority of the evidence was graded at low or very low quality. This was mostly due to selection and performance bias, resulting in a high risk of bias rating, and imprecision.

All evidence was obtained from randomised controlled trial studies. Observational studies were considered, although no studies were identified for comparisons not already addressed by RCTs.

1.7.1.3 Benefits and harms

The committee discussed the evidence on the management of recurrent acute diverticulitis.

The committee noted that there was no evidence to support the use of continuous treatment with aminosalicylate to manage or prevent recurrence of acute diverticulitis. Evidence from one study suggested a positive effect of cyclic aminosalicylate in reducing the risk of recurrent diverticulitis compared to placebo. However, the committee acknowledged that the evidence was of poor quality and with a small study population. The committee added that the evidence appeared to show no dose-response with continuous aminosalicylate therapy in the management of recurrent diverticulitis, indicating no clear physiological benefit of treatment. It was also noted that there was some evidence of harm with continuous aminosalicylate therapy, with evidence showing an increased risk of recurrent diverticulitis with aminosalicylate compared to placebo. The committee added that it is known that aminosalicylate has associated side effects with 1 in 20 people experiencing cramps and abdominal pain with treatment.

The committee agreed that there was no evidence of notable effect of antibiotics on the management or prevention of recurrent diverticulitis. The committee also commented on the use and applicability of the antibiotic utilised in the one study providing evidence for antibiotics in this review – rifaxamin. The committee highlighted that rifaxamin is poorly absorbed and is not routinely prescribed in the UK. The committee also noted that in support of antibiotic stewardship, they would avoid recommending a long or continuous course of antibiotic therapy to avoid antibiotic resistance. However, in the absence of evidence demonstrating clinical benefit or harm no recommendation could be made for antibiotics.

The committee agreed that there was also no evidence of notable effect of probiotics or dietary fibre.

1.7.2 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of management strategies for people with recurrent acute diverticulitis.

The committee highlighted that it is not current practice to use aminosalicylates for recurrent acute diverticulitis and, upon considering the clinical evidence, wished to make a recommendation against using aminosalicylates.

The committee noted that the clinical evidence for antibiotics consisted of one small, low quality study. The study hinted that antibiotics could reduce recurrent diverticulitis and hospitalisation but the effect was not statistically significant. To comply with good practice in antibiotic stewardship, the committee recommended against the use of antibiotics.

1.7.3 Other factors the committee took into account

The committee noted that there has been little evidence to support the use of aminosalicylate therapy in this or other evidence reviews on this guideline, and noted that aminosalicylates are currently not licenced for diverticular disease in the UK.

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Appendices

Appendix A: Review protocols

Table 15: Review protocol: management of recurrent acute diverticulitis

Field	Content
Review question	What is the most clinically and cost effective management strategy for people with recurrent episodes of acute diverticulitis?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine the most clinically and cost effective management strategy for people with recurrent episodes of acute diverticulitis
Eligibility criteria – population / disease / condition / issue / domain	Adults 18 years and over with recurrent acute diverticulitis/in remission from a previous episode of acute diverticulitis at risk of recurrent diverticulitis
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Aminosalicylate • Surgery • Conservative measures - weight loss, exercise, dietary advice • Laxatives • Antibiotics • Probiotics
Eligibility criteria – comparator(s) / control or reference (gold) standard	• RCTs • Observational studies

Outcomes and prioritisation	Critical outcomes:
	
	• Quality of life
	• Mortality
	• Complications
	  ○ infections
	  ○ abscesses
	  ○ perforation
	  ○ fistula
	  ○ stricture
	• Recurrence rates of acute diverticulitis
	• Hospitalisation related to diverticular disease
	• Need for surgery for diverticular disease
	
	Important outcomes:
	• Symptom control: pain relief, bloating, night sweats, fever
	• Side effects of:

	○ antibiotics, nausea and vomiting, antibiotics-related infection ○ analgesics, constipation , nausea and vomiting ○ surgery, morbidity and mortality
Eligibility criteria – study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, search for observational studies
Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger • Prevention
Proposed sensitivity / subgroup analysis, or meta-regression	Strata: Subgroups: • people of Asian family origin as they are known to develop right-sided diverticula • transplant patients/ immunocompromised • age (<50 years and >50 years)
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Bibliographies, citations and study sifting managed using EndNote • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/conditions-and-diseases/digestive-tract-conditions/diverticular-disease
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or G (health economic evidence tables).
Methods for	Standard study checklists were used to critically appraise individual studies.

assessing bias at outcome / study level	For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report (Chapter R) for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by James Dalrymple in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 16: Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health

	economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[28] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:*

	• The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 17: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 13 November 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 11 of 12 CENTRAL to 2018 Issue 11 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Table 18: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/

5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	randomized controlled trial.pt.
23.	controlled clinical trial.pt.
24.	randomi#ed.ti,ab.
25.	placebo.ab.
26.	randomly.ti,ab.
27.	Clinical Trials as topic.sh.
28.	trial.ti.
29.	or/22-28
30.	Meta-Analysis/
31.	exp Meta-Analysis as Topic/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/50-59
41.	Epidemiologic studies/
42.	Observational study/
43.	exp Cohort studies/
44.	(cohort adj (study or studies or analys* or data)).ti,ab.
45.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
46.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
47.	Controlled Before-After Studies/

48.	Historically Controlled Study/
49.	Interrupted Time Series Analysis/
50.	(before adj2 after adj2 (study or studies or data)).ti,ab.
51.	or/30-39
52.	exp case control study/
53.	case control*.ti,ab.
54.	or/41-42
55.	40 or 43
56.	Cross-sectional studies/
57.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	or/45-46
59.	40 or 47
60.	40 or 43 or 47
61.	21 and (29 or 40 or 60)

Table 19: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	random*.ti,ab.
21.	factorial*.ti,ab.
22.	(crossover* or cross over*).ti,ab.
23.	((doubl* or singl*) adj blind*).ti,ab.
24.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
25.	crossover procedure/
26.	single blind procedure/
27.	randomized controlled trial/
28.	double blind procedure/
29.	or/20-28
30.	systematic review/

31.	meta-analysis/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.
37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/30-39
41.	Clinical study/
42.	Observational study/
43.	family study/
44.	longitudinal study/
45.	retrospective study/
46.	prospective study/
47.	cohort analysis/
48.	follow-up/
49.	cohort*.ti,ab.
50.	48 and 49
51.	(cohort adj (study or studies or analys* or data)).ti,ab.
52.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
53.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
54.	(before adj2 after adj2 (study or studies or data)).ti,ab.
55.	or/41-47,50-54
56.	exp case control study/
57.	case control*.ti,ab.
58.	or/56-57
59.	55 or 58
60.	cross-sectional study/
61.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	or/60-61
63.	55 or 62
64.	55 or 58 or 62
65.	19 and (29 or 40 or 64)

Table 20: Cochrane Library (Wiley) search terms

#1.	diverticul*.mp.

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Diverticular Disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 21: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 November 2018 NHSEED - Inception to March 2015	None

Table 22: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20

22.	Economics/
23.	Value of life/
24.	exp "Costs and Cost Analysis"/
25.	exp Economics, Hospital/
26.	exp Economics, Medical/
27.	Economics, Nursing/
28.	Economics, Pharmaceutical/
29.	exp "Fees and Charges"/
30.	exp Budgets/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/22-37
39.	exp models, economic/
40.	*Models, Theoretical/
41.	markov chains/
42.	monte carlo method/
43.	exp Decision Theory/
44.	(markov* or monte carlo).ti,ab.
45.	econom* model*.ti,ab.
46.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
47.	Models, Organizational/
48.	*models, statistical/
49.	*logistic models/
50.	models, nursing/
51.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
52.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
53.	(SSM or SODA).ti,ab.
54.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
55.	soft systems method*.ti,ab.
56.	(Meta-heuristic* or Metaheuristic*).ti,ab.
57.	(dynamic* adj2 (model* or system*)).ti,ab.
58.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
59.	(microsimulation* or "micro* simulation*").ti,ab.
60.	((flow or core) adj2 model*).ti,ab.
61.	(data adj2 envelopment*).ti,ab.
62.	system* model*.ti,ab.
63.	or/41-64
64.	quality-adjusted life years/

65.	sickness impact profile/
66.	(quality adj2 (wellbeing or well being)).ti,ab.
67.	sickness impact profile.ti,ab.
68.	disability adjusted life.ti,ab.
69.	(qal* or qtime* or qwb* or daly*).ti,ab.
70.	(euroqol* or eq5d* or eq 5*).ti,ab.
71.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
72.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
73.	(hui or hui1 or hui2 or hui3).ti,ab.
74.	(health* year* equivalent* or hye or hyes).ti,ab.
75.	discrete choice*.ti,ab.
76.	rosser.ti,ab.
77.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
78.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
79.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
80.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
81.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
82.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
83.	or/22-40
84.	21 and (38 or 63 or 83)

Table 23: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	Economics/

21.	Value of life/
22.	exp "Costs and Cost Analysis"/
23.	exp Economics, Hospital/
24.	exp Economics, Medical/
25.	Economics, Nursing/
26.	Economics, Pharmaceutical/
27.	exp "Fees and Charges"/
28.	exp Budgets/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/20-35
37.	statistical model/
38.	*theoretical model/
39.	nonbiological model/
40.	stochastic model/
41.	decision theory/
42.	decision tree/
43.	exp nursing theory/
44.	monte carlo method/
45.	(markov* or monte carlo).ti,ab.
46.	econom* model*.ti,ab.
47.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
48.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
49.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
50.	(SSM or SODA).ti,ab.
51.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.
52.	soft systems method*.ti,ab.
53.	(Meta-heuristic* or Metaheuristic*).ti,ab.
54.	(dynamic* adj2 (model* or system*)).ti,ab.
55.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
56.	(microsimulation* or "micro* simulation*").ti,ab.
57.	((flow or core) adj2 model*).ti,ab.
58.	(data adj2 envelopment*).ti,ab.
59.	system* model*.ti,ab.

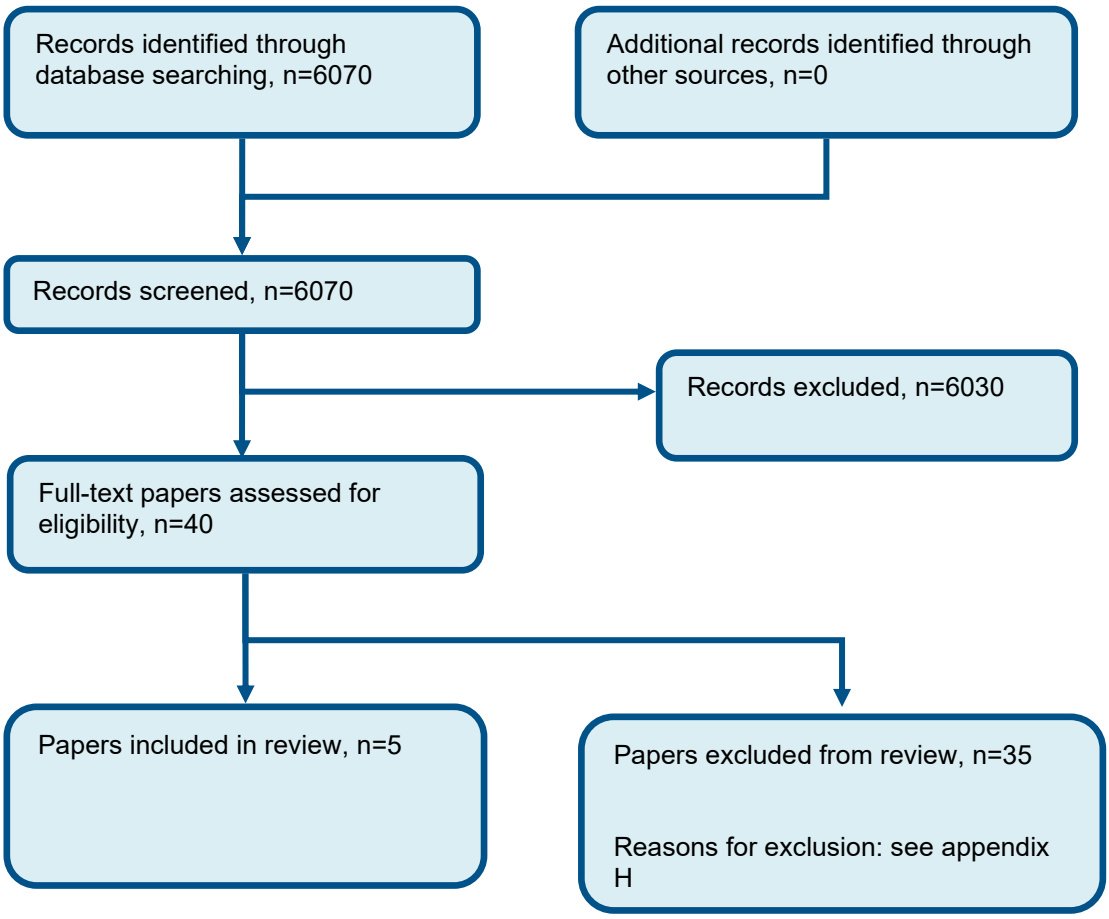
60.	or/39-61
61.	quality adjusted life year/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.
66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.
69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/20-40
83.	19 and (36 or 60 or 82)

Table 24: NHS EED and HTA (CRD) search terms

#1.	diverticul*

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of management of recurrent acute diverticulitis – RCT



Appendix D: Clinical evidence tables

Table 25: Clinical evidence tables

Study	Kruis 2017[24]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	2 (n=345)
Countries and setting	Conducted in Germany; Setting: specialised gastroenterology centres
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 96 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults who had a prior diagnosis of left-sided uncomplicated acute diverticulitis confirmed by ultrasonography or computed tomography (CT) with at least one diverticulum in the left colon the prior episode of left-sided uncomplicated diverticulitis was within the preceding 6 months and has been brought to clinical remission with antibiotics and/or dietary modification, documented by medical records, (4)they had ≥3 of the following symptoms at the start of the most recent episode of diverticulitis: left lower quadrant pain, fever, altered bowel habit(diarrhoea, constipation, passage of mucus, or urgency) and systemic signs(nausea, lethargy), (5) C-reactive protein (CRP) exceeded the upper limit of normal (ULN) or leucocytosis (>10 000/mm3) at the start of the most recent episode.
Exclusion criteria	Patients with chronic inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) were excluded. Additional exclusion criteria included complicated diverticulitis (diverticulitis with associated abscess, fistula, obstruction or perforation), right-sided diverticulitis, previous colonic surgery, symptomatic organic disease of the GI tract, active colorectal cancer or history of colorectal cancer, active malignancy other than colorectal cancer or treatment with anticancer drugs during the previous 5 years, haemorrhagic diathesis, active peptic ulcer disease, local intestinal infection, asthma without careful medical monitoring, abnormal

	hepatic function or liver cirrhosis, abnormal renal function, severe co-morbidity and/or immobility and known intolerance/hypersensitivity/resistance to study drug or drugs of similar chemical structure. Patients who had received mesalazine-containing drugs, glucocorticosteroids, opioid analgesics, laxatives, antidiarrhoeals, immunosuppressants or non-steroidal anti-inflammatory drugs after the most recent episode were also excluded.
Recruitment/selection of patients	Recruited from clinic
Age, gender and ethnicity	Age - Other: < 60 years: 122, > 60 years: 89. Gender (M:F): 94/117. Ethnicity: NA
Further population details	
Indirectness of population	No indirectness
Interventions	(n=263) Intervention 1: Aminosalicylates. mesalazine 3.0g once daily. Duration 48-96 weeks. Concurrent medication/care: NA. Indirectness: No indirectness (n=125) Intervention 2: Aminosalicylates. mesalazine 1.5g once daily. Duration 96 weeks. Concurrent medication/care: NA. Indirectness: No indirectness (n=287) Intervention 3: No intervention/placebo - Placebo. Placebo. Duration 48-96 weeks. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Study funded by industry (funded in full by Dr. Falk Pharma GmbH)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE (3G/D) versus MESALAZINE (1.5G/D)

Protocol outcome 1: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Diverticulitis recurrence at 48 weeks; Group 1: 89/240, Group 2: 47/87
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 70; Group 2 Number missing: 46

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE (3G/D) versus PLACEBO

Protocol outcome 1: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Diverticulitis recurrence at 48 weeks; Group 1: 89/240, Group 2: 77/249

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 70; Group 2 Number missing: 40 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAZINE (1.5G/D) versus PLACEBO Protocol outcome 1: Recurrence rates of acute diverticulitis at Define - Actual outcome: Diverticulitis recurrence at 48 weeks; Group 1: 47/87, Group 2: 77/249 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 46; Group 2 Number missing: 70	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Hospitalisation at Define; Symptom control (pain relief) at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	Lanas 2013[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=165)
Countries and setting	Conducted in Spain; Setting: Multicentre
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Recent episodes confirmed by CT scan, ultrasonography or endoscopy.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients aged ≥18 years with one or more recent (within the previous two months) episodes of acute diverticulitis but in remission at the time of enrolment. Recent episodes confirmed by CT scan, ultrasonography or endoscopy.
Exclusion criteria	Patients with acute episodes at recruitment, history of intolerance or allergy to rifaximin or study drugs, cancer, immunodepressed, severe renal, hepatic or cardiac insufficiency.
Recruitment/selection of patients	Enrolled by the attending physician.
Age, gender and ethnicity	Age - Mean (SD): 54.1 (12.5). Gender (M:F): 106/59. Ethnicity: NA
Further population details	
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Antibiotics. 2 tablets of rifaximin polymorph alpha b.d. (total 800 mg per day) for the first week of each 4 week period. Duration 48 weeks. Concurrent medication/care: All patients received 3.5g b.d. of plantago ovata husk (dietary fibre) taken daily for the entirety of the study.. Indirectness: No indirectness (n=88) Intervention 2: No intervention/placebo - No intervention. Dietary fibre only. Duration 48 weeks. Concurrent medication/care: All patients received 3.5g b.d. of plantago ovata husk (dietary fibre) taken daily for the entirety of the study.. Indirectness: No indirectness

Funding	Study funded by industry (BAMA-GEVE)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANTIBIOTICS + FIBRE versus DIETARY FIBRE Protocol outcome 1: Hospitalisation related to acute diverticulitis at Define - Actual outcome: Hospitalisation at 48 weeks; Group 1: 2/77, Group 2: 6/88 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 21; Group 2 Number missing: 12 Protocol outcome 2: Symptom control (pain relief) at Define - Actual outcome: Symptom intensity at 48 weeks; Group 1: mean 3.45 (SD 7.03); n=77, Group 2: mean 3.26 (SD 5.81); n=88; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 21; Group 2 Number missing: 12 Protocol outcome 3: Recurrence rates of acute diverticulitis at Define - Actual outcome: Recurrence of diverticulitis at 48 weeks; Group 1: 8/77, Group 2: 17/88 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 21; Group 2 Number missing: 12	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Complications (fistula) at Define; Complications (stricture) at Define; Progression of disease at Define

Study	Raskin 2014[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=1182)
Countries and setting	Conducted in USA; Setting: Multi-centre
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A report confirming an earlier episode of diverticulitis was required and could include computed tomography, magnetic resonance imaging, ultrasound, colonoscopy, sigmoidoscopy, and barium enema.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were 18 years of age or older with ≥1 documented episodes of acute diverticulitis in the previous 24 months that resolved without colonic resection, and without signs or symptoms of diverticulitis within 6 weeks of enrolment.
Exclusion criteria	Exclusion criteria included previous colorectal surgery, including surgical intervention for diverticular disease (with the exceptions of hemorrhoidectomy, colonic removal of polyps, and appendectomy); no complicated diverticulitis (no perforation or fistulization present on CT); right-sided diverticulosis only; active peptic ulcer disease; and history or current presence of inflammatory bowel disease. Patients with active irritable bowel syndrome, gastrointestinal bleeding, endometriosis or dysmenorrhea (≤6 months before baseline), or current or historical use of biologic drugs (i.e., anti–tumor necrosis factor agents), immunomodulators, or systemic/rectal steroids (≤6 weeks before baseline) were also excluded.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 55.7 (11). Gender (M:F): 580/389. Ethnicity: NA
Further population details	
Extra comments	A report confirming an earlier episode of diverticulitis was required and could include computed tomography, magnetic resonance imaging, ultrasound, colonoscopy, sigmoidoscopy, and barium enema.
Indirectness of population	No indirectness

Interventions	(n=299) Intervention 1: Aminosalicylates. Mesalamine 4.8g daily (four 1.2-g tablets). Duration 24 months. Concurrent medication/care: NA. Indirectness: No indirectness (n=290) Intervention 2: Aminosalicylates. Mesalamine 2.4g daily (two 1.2-g tablets plus two placebo tablets). Duration 24 months. Concurrent medication/care: NA. Indirectness: No indirectness (n=291) Intervention 3: Aminosalicylates. Mesalamine 1.2g daily (one 1.2-g tablets plus three placebo tables). Duration 24 months. Concurrent medication/care: NA. Indirectness: No indirectness (n=289) Intervention 4: No intervention/placebo - Placebo. 4 placebo tablets daily. Duration 24 months. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Study funded by industry (Shire Development LLC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAMINE (4.8G/D) versus MESALAMINE (2.4G/D)

Protocol outcome 1: Quality of life at Define
- Actual outcome: EQ-5D at 104 weeks; Overall, the EQ-5D result revealed no patterns or trends across study arms at baseline or week 104. ;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Need for surgery at Define
- Actual outcome: Patients requiring surgery for diverticular disease at 104 weeks; Group 1: 5/268, Group 2: 6/265
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 29

Protocol outcome 3: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Recurrence of diverticulitis at 104 weeks; Group 1: 80/268, Group 2: 80/261
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 31; Group 2 Number missing: 29

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAMINE (4.8G/D) versus MESALAMINE (1.2G/D)

Protocol outcome 1: Need for surgery at Define
- Actual outcome: Patients requiring surgery for diverticular disease at 104 weeks; Group 1: 5/268, Group 2: 6/265
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 26

Protocol outcome 2: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Recurrence of diverticulitis at 104 weeks; Group 1: 80/268, Group 2: 77/265
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Withdrawal considered as recurrence.; Group 1 Number missing: 31; Group 2 Number missing: 26

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAMINE (4.8G/D) versus PLACEBO

Protocol outcome 1: Need for surgery at Define
- Actual outcome: Patients requiring surgery for diverticular disease at 104 weeks; Group 1: 5/268, Group 2: 2/257
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31; Group 2 Number missing: 32

Protocol outcome 2: Recurrence rates of acute diverticulitis at Define
- Actual outcome: Recurrence of diverticulitis at 104 weeks; Group 1: 117/299, Group 2: 101/289
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Withdrawal considered as recurrence.; Group 1 Number missing: 31; Group 2 Number missing: 32

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAMINE (2.4G/D) versus MESALAMINE (1.2G/D)

Protocol outcome 1: Need for surgery at Define
- Actual outcome: Patients requiring surgery for diverticular disease at 104 weeks; Group 1: 4/261, Group 2: 6/265
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 26

Protocol outcome 2: Recurrence rates of acute diverticulitis at Define

- Actual outcome: Recurrence of diverticulitis at 104 weeks; Group 1: 80/261, Group 2: 77/265 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Withdrawal considered as recurrence.; Group 1 Number missing: 29; Group 2 Number missing: 26 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAMINE (2.4G/D) versus PLACEBO Protocol outcome 1: Need for surgery at Define - Actual outcome: Patients requiring surgery for diverticular disease at 104 weeks; Group 1: 4/261, Group 2: 2/257 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 32 Protocol outcome 2: Recurrence rates of acute diverticulitis at Define - Actual outcome: Recurrence of diverticulitis at 104 weeks; Group 1: 113/290, Group 2: 101/289 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Withdrawal considered as recurrence.; Group 1 Number missing: 29; Group 2 Number missing: 32 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MESALAMINE (1.2G/D) versus PLACEBO Protocol outcome 1: Need for surgery at Define - Actual outcome: Patients requiring surgery for diverticular disease at 104 weeks; Group 1: 6/265, Group 2: 2/257 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26; Group 2 Number missing: 32 Protocol outcome 2: Recurrence rates of acute diverticulitis at Define - Actual outcome: Recurrence of diverticulitis at 104 weeks; Group 1: 109/291, Group 2: 101/289 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Withdrawal considered as recurrence.; Group 1 Number missing: 26; Group 2 Number missing: 32	
Protocol outcomes not reported by the study	Hospitalisation related to acute diverticulitis at Define; Symptom control (pain relief) at Define; Mortality at Define: Side effects of antibiotics: nausea and vomiting at Define: Side effects of antibiotics: diarrhoea at

Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Complications (fistula) at Define; Complications (stricture) at Define; Progression of disease at Define	

Study	Parente 2013[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=96)
Countries and setting	Conducted in Italy; Setting: Outpatients of gastroenterological unit
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 18 and 85 years, endoscopic and/or radiologic evidence of diverticular disease of the left colon (already known before the uncomplicated diverticulitis episode or confirmed within the subsequent months), documented episode of uncomplicated diverticulitis during the last months (maximum 12 months), recruitment which was considered possible only after the complete clinical remission of diverticulitis flare and presence of symptoms attributable to diverticular disease of the colon such as upper and/or lower abdominal pain/discomfort, bloating, tenesmus, diarrhoea, abdominal tenderness, nausea, emesis, fever, dysuria and bleeding.
Exclusion criteria	Exclusion criteria were the following: complicated diverticulitis(fistulas, stenosis, abscesses and/or bleeding), previous colonic surgery, ascertained hypersensitivity to the salicylates, any severe pathology that could interfere with the treatment or the clinical or instrumental test of the trial, clinically significant renal or hepatic impairment, oesophageal, gastric or duodenal ulcer within 30 days prior to randomisation, patients with active malignancy of any type or history of a malignancy (patients with history of malignancies that had been surgically removed and who had no evidence of recurrence for at least 5 years before study enrolment were also acceptable), treatment with any investigational drug within 30 days before enrolment, treatment with lactulose or with any compound that lowering the colonic pH could prevent the release of the active moiety from the tablets, recent history or suspicion of alcohol abuse or drug addiction, patients who became unable to conform to protocol, women with ascertained pregnancy and a questionable ability to cooperate.
Recruitment/selection of patients	Outpatients recruited

Age, gender and ethnicity	Age - Mean (SD): 61.5. Gender (M:F): 45/47. Ethnicity: NA
Further population details	
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Aminosalicylates. Mesalazine (Pentacol®) 800 mg one tablet bid for 10 days every month. Duration 24 months. Concurrent medication/care: NA. Indirectness: No indirectness (n=47) Intervention 2: No intervention/placebo - Placebo. Identically appearing placebo (placebo-treated group) one tablet bid for 10 days every month. Duration 24 months. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Study funded by industry (SOFAR)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOSALICYLATES versus PLACEBO Protocol outcome 1: Recurrence rates of acute diverticulitis at Define - Actual outcome: Risk of relapse incidence at 24 months; RR; 0.49 (95%CI 0.202 to 1.187) (p: 0.1011) ; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8; Group 2 Number missing: 8	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Hospitalisation at Define; Symptom control (pain relief) at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Side effects of analgesics: nausea and vomiting at Define; Side effects of analgesics: constipation at Define; Side effects of antispasmodics: AF at Define; Progression of disease at Define

Study	Tursi 2007[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Italy; Setting: Outpatient setting
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients affected by uncomplicated acute diverticulitis, diagnosis of uncomplicated diverticulitis, defined as symptomatic diverticular disease with signs of inflammation (increased erythrocyte sedimentation rate and/or increased C-reactive protein and/or increased white cells count) but without complications, confirmed by colonoscopy.
Exclusion criteria	Recent antibiotic treatment (<2 weeks), active or recent peptic ulcer, chronic renal insufficiency, allergy to salicylates and other diverticulitis complications (fistulas, abscesses and/or haemorrhage).
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (range): 60.1 (47-75). Gender (M:F): 19/11. Ethnicity: NA
Further population details	
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Aminosalicylates. Balsalazide 2.25 g for 10 days/month plus VSL#3 450 billions/day for 15 days every month as 1 bag containing viable lyophilised bacteria.. Duration 12 months. Concurrent medication/care: All patients received for the first 10 days: balsalazide 2.25 g daily plus rifaximin 800 mg/day to achieve remission. Indirectness: No indirectness (n=15) Intervention 2: Probiotics/prebiotics - Probiotics. VSL#3 450 billions/day for 15 days every month as 1 bag containing viable lyophilised bacteria.. Duration 12 months. Concurrent medication/care: All patients

	received for the first 10 days: balsalazide 2.25 g daily plus rifaximin 800 mg/day to achieve remission. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOSALICYLATES + PROBIOTIC versus PROBIOTICS Protocol outcome 1: Symptom control (pain relief) at Define - Actual outcome: Abdominal pain at 12 months; Abdominal pain scores at the end of follow-up were statistically significantly lower in balsalazide/VSL#3 group than in VSL#3 alone group.; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1 Protocol outcome 2: Recurrence rates of acute diverticulitis at Define - Actual outcome: Recurrent diverticulitis at 12 months; Group 1: 1/15, Group 2: 2/15; Comments: Acute uncomplicated diverticulitis recurrence was evaluated on the basis of clinical (recurrence or new impairment, abdominal pain and/or bowel habit disorders, presence of fever) and/or endoscopical (inflamed mucosa and/or presence of complications, such as stenoses, associated to the diverticula of the colon) examination. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life at Define; Need for surgery at Define; Hospitalisation related to acute diverticulitis at Define; Mortality at Define; Side effects of antibiotics: nausea and vomiting at Define; Side effects of antibiotics: diarrhoea at Define; Side effects of antibiotics: infections related to antibiotics at Define; Complications (infections) at Define; Complications (abscesses) at Define; Complications (perforation) at Define; Complications (fistula) at Define; Complications (stricture) at Define; Progression of disease at Define

Appendix E: Forest plots

E.1 Aminosalicylate (4.8g/d) compared to aminosalicylate (2.4g/d)

Figure 2: Recurrent diverticulitis

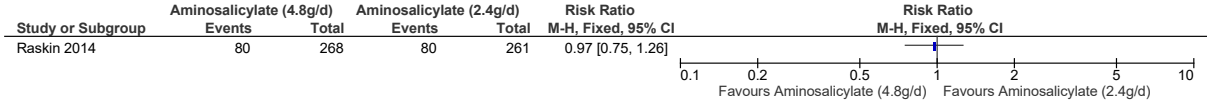
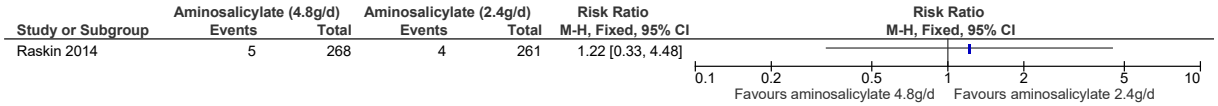


Figure 3: Surgery



E.2 Aminosalicylate (4.8g/d) compared to aminosalicylate (1.2g/d)

Figure 4: Recurrent diverticulitis

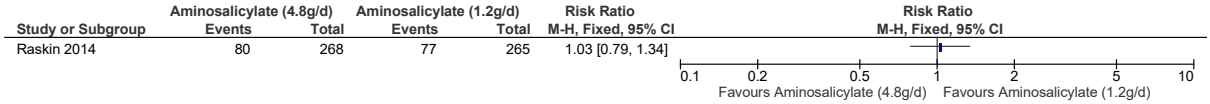
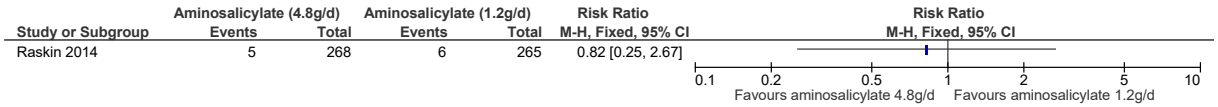


Figure 5: Surgery



E.3 Aminosalicylate (3g/d) compared to aminosalicylate (1.5g/d)

Figure 6: Recurrent diverticulitis

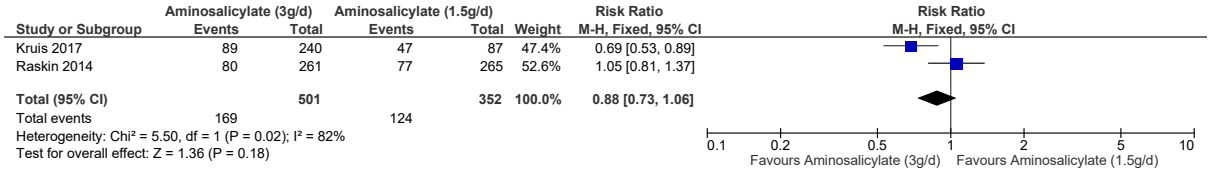
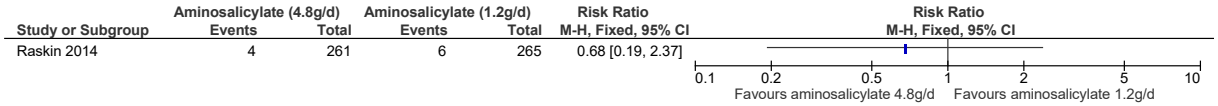


Figure 7: Surgery



E.4 Aminosalicylate (4.8g/d) compared to placebo

Figure 8: Recurrent diverticulitis

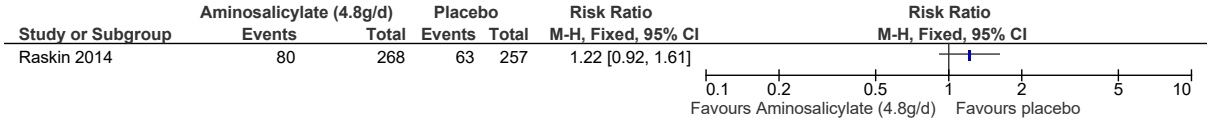
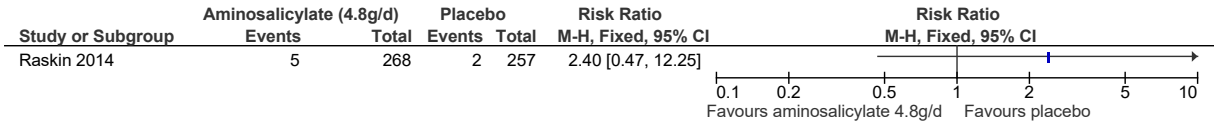


Figure 9: Surgery



E.5 Aminosalicylate (3g/d) compared to placebo

Figure 10: Recurrent diverticulitis

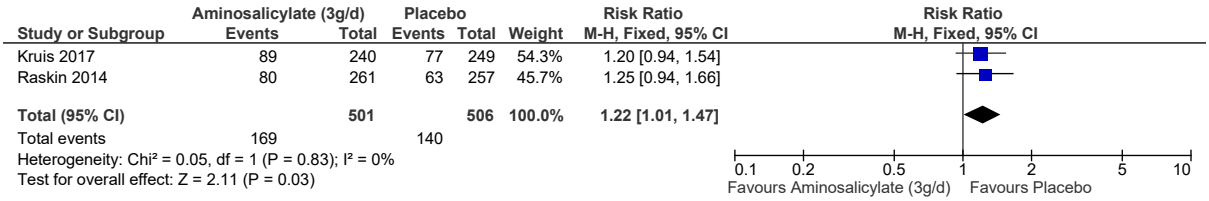
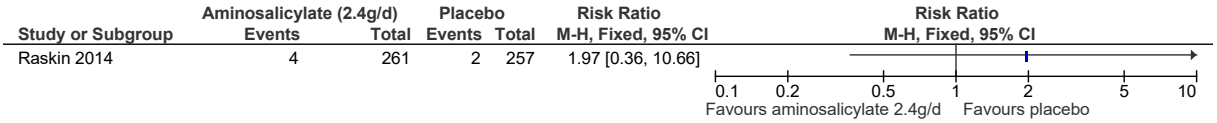


Figure 11: Surgery



E.6 Aminosalicylate (1.5g/d) compared to placebo

Figure 12: Recurrent diverticulitis

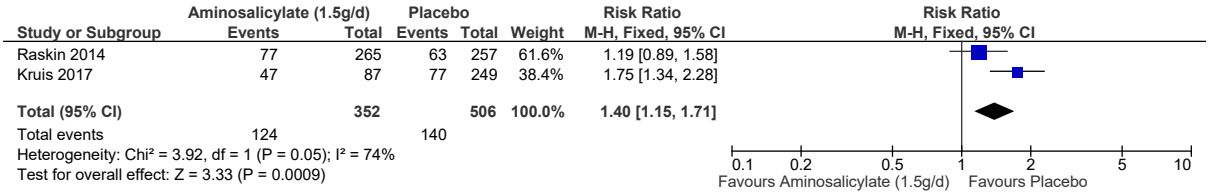
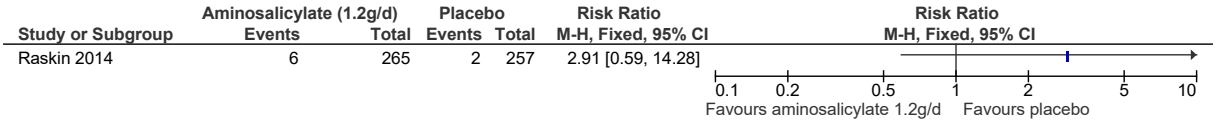
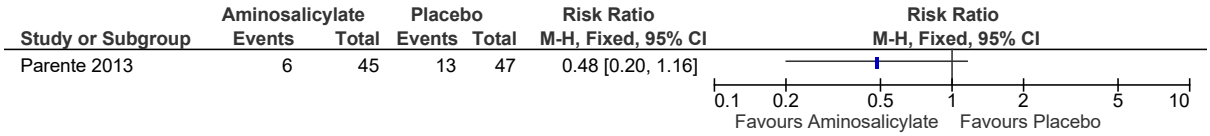


Figure 13: Surgery



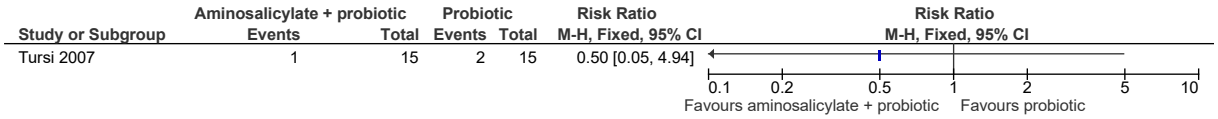
E.7 Aminosalicylate (cyclic) compared to placebo

Figure 14: Recurrent diverticulitis



E.8 Aminosalicylate + probiotic compared to probiotic

Figure 15: Recurrent diverticulitis



E.9 Antibiotic + dietary fibre compared to dietary fibre

Figure 16: Recurrent diverticulitis

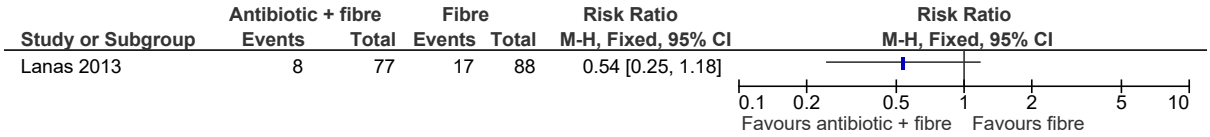


Figure 17: Hospitalisation

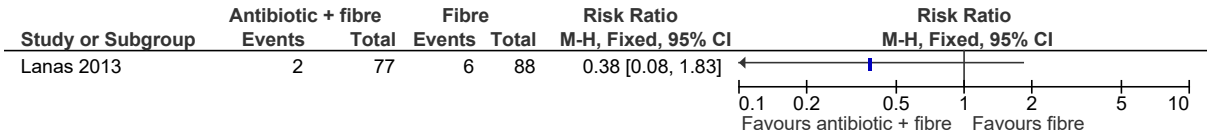
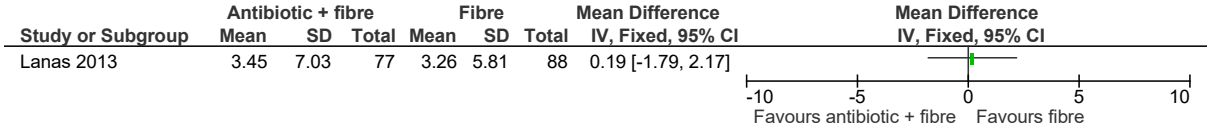


Figure 18: Symptoms (intensity)



Appendix F: GRADE tables

Table 26: Clinical evidence profile: Aminosalicylate (4.8g/d) compared to aminosalicylate (2.4g/d) recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate (4.8g/d)	Aminosalicylate (2.4g/d)	Relative (95% CI)	Absolute		
Recurrent diverticulitis (follow-up mean 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	80/268 (29.9%)	30.7%	RR 0.97 (0.75 to 1.26)	9 fewer per 1000 (from 77 fewer to 80 more)	⊕⊕OO LOW	CRITICAL
Surgery (follow-up mean 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/268 (1.9%)	1.5%	RR 1.22 (0.33 to 4.48)	3 more per 1000 (from 10 fewer to 52 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 27: Clinical evidence profile: Aminosalicylate (4.8g/d) compared to aminosalicylate (1.2g/d) recurrent diverticulitis

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate (4.8g/d)	Aminosalicylate (1.2g/d)	Relative (95% CI)	Absolute		
Recurrent diverticulitis (follow-up mean 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	80/268 (29.9%)	29.1%	RR 1.03 (0.79 to 1.34)	9 more per 1000 (from 61 fewer to 99 more)	⊕⊕OO LOW	CRITICAL
Surgery (follow-up mean 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/268 (1.9%)	2.3%	RR 0.82 (0.25 to 2.67)	4 fewer per 1000 (from 17 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 28: Clinical evidence profile: Aminosalicylate (3g/d) compared to aminosalicylate (1.5g/d) recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylate (3g/d)**	**Aminosalicylate (1.5g/d)**	**Relative (95% CI)**	**Absolute**		
Recurrent diverticulitis (follow-up 1-2 years)												
2	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[2]	none	169/501 (33.7%)	41.5%	RR 0.88 (0.73 to 1.37)	50 fewer per 1000 (from 112 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL

Surgery (follow-up mean 2 years)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/261 (1.5%)	2.3%	RR 0.68 (0.19 to 2.37)	7 fewer per 1000 (from 19 fewer to 32 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p<0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 29: Clinical evidence profile: Aminosalicylate (4.8g/d) compared to placebo recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylate (4.8g/d)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Recurrent diverticulitis (follow-up mean 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	80/268 (29.9%)	24.5%	RR 1.22 (0.92 to 1.61)	54 more per 1000 (from 20 fewer to 149 more)	⊕⊕⊕O MODERATE	CRITICAL
Surgery (follow-up mean 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/268 (1.9%)	0.8%	RR 2.4 (0.47 to 12.25)	11 more per 1000 (from 4 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 30: Clinical evidence profile: Aminosalicylate (3g/d) compared to placebo recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate (3g/d)	Placebo	Relative (95% CI)	Absolute		
Recurrent diverticulitis (follow-up 1-2 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	169/501 (33.7%)	27.7%	RR 1.22 (1.01 to 1.47)	61 more per 1000 (from 3 more to 130 more)	⊕⊕⊕O MODERATE	CRITICAL
Surgery (follow-up mean 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/261 (1.5%)	0.8%	RR 1.97 (0.36 to 10.66)	8 more per 1000 (from 5 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 31: Clinical evidence profile: Aminosalicylate (1.5g/d) compared to placebo recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate (1.5g/d)	Placebo	Relative (95% CI)	Absolute		

Recurrent diverticulitis (follow-up 1-2 years)											
2	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	124/352 (35.2%)	27.7%	RR 1.4 (1.15 to 1.71)	111 more per 1000 (from 42 more to 197 more)	⊕⊕OO LOW	CRITICAL
Surgery (follow-up mean 2 years)											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/265 (2.3%)	0.8%	RR 2.91 (0.59 to 14.28)	15 more per 1000 (from 3 fewer to 106 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p<0.04, unexplained by subgroup analysis.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 32: Clinical evidence profile: Aminosalicylate (cyclic) compared to placebo recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aminosalicylate (cyclic)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Recurrent diverticulitis (follow-up mean 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/45 (13.3%)	27.7%	RR 0.48 (0.2 to 1.16)	144 fewer per 1000 (from 222 fewer to 44 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 33: Clinical evidence profile: Aminosalicylate + probiotic compared to probiotic for recurrent diverticulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aminosalicylate + probiotic	Probiotic	Relative (95% CI)	Absolute		
Recurrent diverticulitis (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/15 (6.7%)	13.3%	RR 0.5 (0.05 to 4.94)	67 fewer per 1000 (from 126 fewer to 524 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Table 34: Clinical evidence profile: Antibiotic + fibre compared to fibre for recurrent diverticulitis

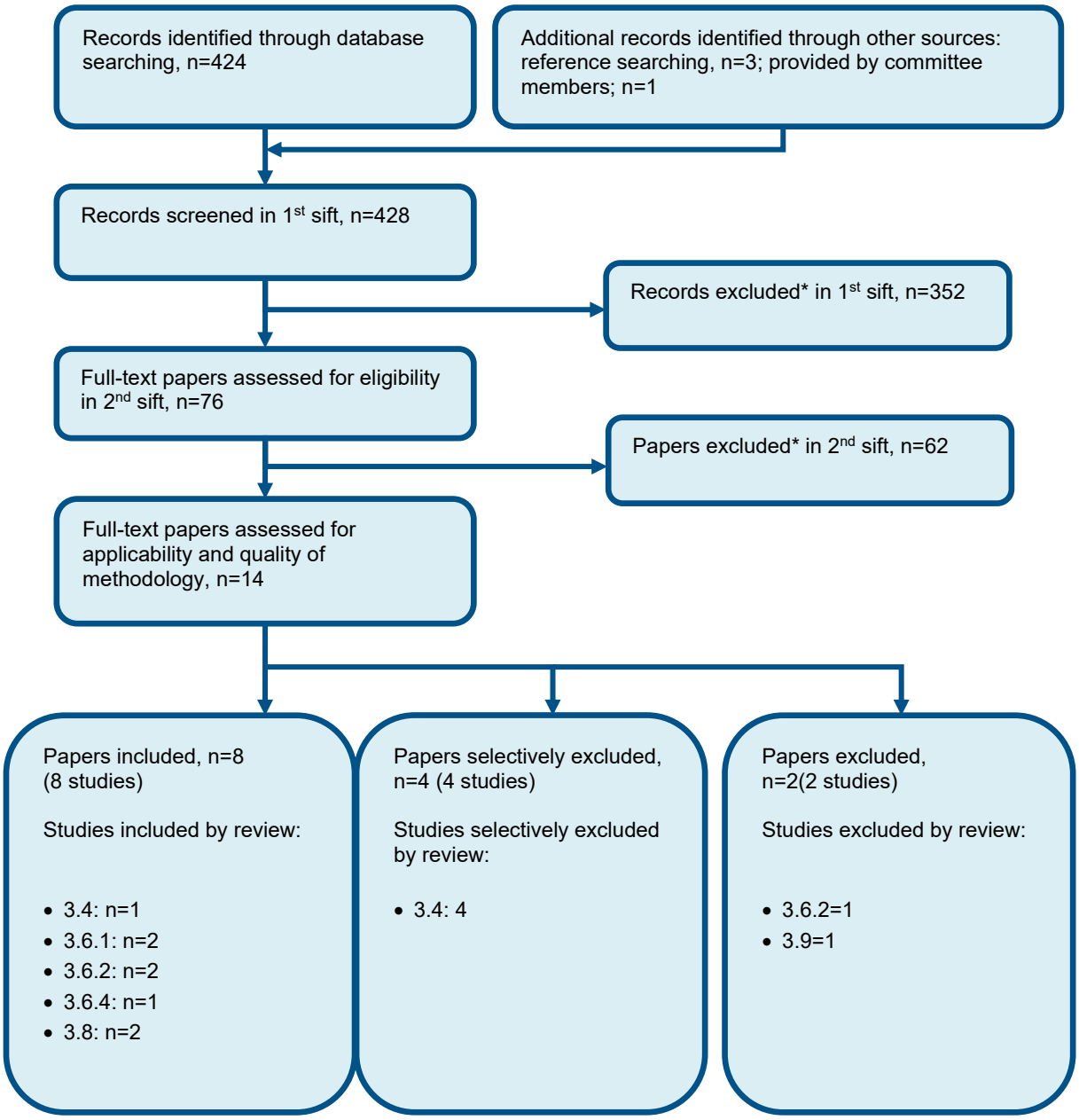
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic + fibre	Fibre	Relative (95% CI)	Absolute		
Recurrent diverticulitis (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/77 (10.4%)	19.3%	RR 0.54 (0.25 to 1.18)	89 fewer per 1000 (from 145 fewer to 35 more)	⊕⊕OO LOW	CRITICAL

Hospitalisation (follow-up mean 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/77 (2.6%)	6.8%	RR 0.38 (0.08 to 1.83)	42 fewer per 1000 (from 63 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Symptoms (intensity) (follow-up mean 1 years; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	77	88	-	MD 0.19 higher (1.79 lower to 2.17 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 19: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3.4 Non-surgical treatment of acute diverticulitis (Evidence review H)

3.6.1 Timing of surgery (Evidence review J)

3.6.2 Laparoscopic versus open resection (Evidence review K)

3.6.4 Primary versus secondary anastomosis (Evidence review M)

3.8 Laparoscopic lavage versus resection for perforated diverticulitis (Evidence review O)

3.9 Management of recurrent diverticulitis (Evidence review P)

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 35: Excluded clinical studies

Study	Exclusion reason
Alamili 2009[1]	Not review population
Andeweg 2016[2]	SR not relevant PICO
Binda 2012[4]	No comparison group
Boudart 2008[5]	Not review population
Buchanan 2002[6]	Incorrect study design
Carter 2017[7]	Not review population
Chabok 2012[8]	Not review population
Chabok 2013[9]	Not in English
Chapman 2005[10]	No comparison group
Comparato 2007[11]	Not review population
Eglinton 2010[12]	No comparison group
Floch 2006[13]	Incorrect study design
Floch 2008[14]	Incorrect study design
Frattini 2006[15]	Incorrect study design
Frileux 2010[16]	No comparison group
Hoffmann 2012[17]	Inappropriate comparison
Humes 2016[18]	Not review population
Hupfeld 2017[19]	Incorrect study design
Issa 2009[20]	Inappropriate comparison
Khan 2016[21]	Not review population
Khan 2017[22]	Inappropriate comparison
Klarenbeek 2009[23]	Not review population
Martinez 2011[27]	Conference abstract
Parnaby 2016[30]	Conference abstract
Pittet 2009[31]	Inappropriate comparison
Ragupathi 2011[32]	No comparison group
Ribas 2010[34]	Not review population
Sallinen 2015[35]	Incorrect interventions. Inappropriate comparison
Schwandner 2004[36]	No comparison group
Sher 1997[37]	Not review population
Thomas 2013[38]	Not review population
Tursi 2002[39]	Confounders not adjusted for
Tursi 2016[41]	Incorrect study design
Wijaya 2011[42]	Conference abstract
Wijaya 2012[43]	Conference abstract

H.2 Excluded health economic studies

Table 36: Studies excluded from the health economic review

Reference	Reason for exclusion
Andeweg 2016 [3] (The Netherlands)	The Markov model in this study calculated QALYs but did not calculate costs. It was assessed as not applicable.