National Institute for Health and Care Excellence

Draft

Ulcerative colitis

Evidence reviews for induction of remission in mild-to-moderate ulcerative colitis

NICE guideline <number>

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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ISBN:

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Induction of remission in mild-to-moderate ulcerative colitis

Review question

In adults, children and young people with mild-to-moderate ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates, immunomodulators (methotrexate, mycophenolate and tacrolimus) for the induction of remission compared to themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?

Introduction

Ulcerative colitis is a chronic inflammatory disease of the rectum and colon characterised by mucosal inflammation, resulting in symptoms of diarrhoea (both soft stool and an increased frequency of defaecation), rectal bleeding, an urgent need to defaecate and abdominal pain.

The natural course of ulcerative colitis is characterised by periods where symptoms are present, interspersed with periods of clinical remission. The severity of the symptoms, when present, can vary from mild to severe. The most severe form was defined by Truelove and Witts as those with a high stool frequency associated with systemic features including fever, tachycardia, anaemia or a raised erythrocyte sedimentation rate (ESR). Mild attacks are defined as those where the stool frequency is less than four times per day, with only small amounts of blood. Moderate attacks are those where the severity is between mild and severe. Treatment of these exacerbations – induction of remission – may involve a range of different drug types, administered by different routes and at different doses.

In 2017, the NICE Surveillance team reviewed evidence on the induction of remission in people with mild-to-moderate ulcerative colitis. New evidence was found for the treatment options included in the review, including budesonide multimatrix (MMX), which was licensed in 2014 for inducing remission in mild-to-moderate ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient. Additionally, new evidence was available on topical preparations. This review aims to consider aminosalicylates, corticosteroids and immunomodulators for the induction of remission in mild-to-moderate ulcerative colitis. Oral and topical preparations were considered, and subcutaneous was considered for methotrexate only. For full details of the review protocol, see Appendix A:

PICO table

Table 1: PICO table

Population	Included: Adults (18 years and older), young people and children with a diagnosis of mild-to-moderate (author defined) ulcerative colitis. Excluded: Mixed IBD populations where the results are not displayed separately for ulcerative colitis. People with indeterminate or idiopathic colitis. Chronic active ulcerative colitis. Inflammatory bowel disease-undefined (IBD-U) and colitis. Greater than 10% of the study population has severe ulcerative colitis (author defined).

Interventions

Corticosteroids	Prednisolone (alone only when Aminosalicylates not tolerated)
	Hydrocortisone
	Budesonide (alone only when Aminosalicylates not tolerated)
	Beclometasone (alone only when Aminosalicylates not tolerated)
Aminosalicylates	Mesalazine
	Olsalazine
	Balsalazide
	Sulphasalazine
Immunomodulators	Methotrexate
	Tacrolimus
	Mycophenolate
Placebo	

Excluded

- Azathioprine and Mercaptopurine – excluded as both considered to be for maintenance of remission rather than induction.
- Hydrocortisone, Beclometasone and Budesonide excluded for children but included for adults.

The doses included are those considered effective for inducing remission for an acute exacerbation of ulcerative colitis.

Only drug treatments and preparations available in the UK are included.

Comparator

- Placebo
- Interclass comparisons
- Combinations of drugs
- Dose

Outcomes	RRs will be used for outcomes
	• Clinical remission (author defined) at
	  ○ < 2weeks
	  ○ 2 to < 4 weeks
	  ○ 4 to < 6 weeks
	  ○ 6 to < 8weeks
	  ○ >8 weeks to 12 weeks[1]
	• Withdrawal due to adverse events
	• Quality of life

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A. Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

For full details of methods and processes, see Appendix B.

Stratification of studies by extent of disease

Evidence was stratified in accordance to extent of disease, as reported in the study:

- Proctitis
- Proctosigmoiditis or left-sided disease
- Extensive disease

Where available, evidence on subgroups of different extents of disease was taken from a study. Where a study did not include subgroups of extents of disease and included a population of participants with different extents of disease, the study was classified under the extent of disease in most (50% or more) of the population. In some studies, extent of disease was only provided in terms of distance away from the anal verge, as confirmed by sigmoidoscopy. In these cases extent of disease was defined as:

- Proctitis: < 15 cm
- Proctosigmoiditis or left-sided: 15 – 50cm
- Extensive: >50cm

Stratification of drugs by dose

Drugs were stratified into 'high dose' and 'standard dose' (also referred to as 'low dose' in many studies[2]). See Table 2 for criteria used to define standard and high drug dose. The committee did not specify a standard and high-dose criteria for oral corticosteroids. However, studies reporting on corticosteroids did not exceed 9mg budesonide, 5mg beclomethasone and up to 60mg prednisolone. The committee agreed that this was in accordance with clinical practice.

[1] A trial duration limit of 12 weeks was applied. It was thought that any drug taking longer than 12 weeks to have an effect would not be suitable for the induction of remission and was more likely to be maintenance of remission treatment.

[2] The committee agreed that the doses given in studies as 'low dose' coincided with the standard dose given in clinical practice.

Table 2: Dosing criteria

		Standard dose	High dose
Corticosteroids	Prednisolone (alone only when Aminosalicylates not tolerated)	No criteria specified.	No criteria specified.
	Hydrocortisone	No criteria specified.	No criteria specified.
	Budesonide (alone only when Aminosalicylates not tolerated)	Adults: 9mg per day	Adults: over 9mg per day
	Beclometasone (alone only when Aminosalicylates not tolerated)	No criteria specified.	No criteria specified.
Aminosalicylates	Mesalazine	Asacol and octasa: 2.4 – <4.8g/day Pentasa: up to 2g/day Salofalk granules: up to 1.5g/day	Asacol and octasa: 4.8g/day Pentasa: 4g/day or over Salofalk granules: 3g/day or over
	Olsalazine	Up to 3g/day	3g/day and over
	Balsalazide	< 6.75g/day	6.75g/day and over*
	Sulphasalazine	4 to 6g/day	Over 6g/day
Immunomodulators	Methotrexate	No criteria specified.	No criteria specified
	Tacrolimus		
	Mycophenolate		
Placebo			

**Note that one study (Scherl 2009) reported a daily dose of 6.6g/day of Balsalazide. This was considered equivalent to 6.75g and was classified as high dose.*

Protocol deviations

The effects estimates measure for outcomes chosen in this review was odds ratios (ORs) or hazard ratios (HRs), which deviates from the protocol's specification of risk ratios (RRs). This is because the estimates produced from the network meta-analysis required for health economic modelling were ORs. To be consistent, ORs were also produced for the pairwise meta-analysis.

The committee considered remission, complete remission and clinical remission as equivalent and direct evidence. However, it was agreed that the definition of clinical response may differ in identified evidence, and this was excluded.

The protocol specified that outcomes will be stratified by extent of disease. This was the case for clinical remission and quality of life. However, for withdrawal due to adverse events, the committee specified interest in finding which interventions had the highest overall withdrawal due to adverse events. Therefore, this outcome was not stratified by extent of disease.

Follow-up times

Due to the availability of evidence and study reporting, clinical remission was stratified by extent of disease and the following follow-up times in the pairwise analysis:

- 0 to 2 weeks,
- 3 to 4 weeks,
- 5 to 8 weeks,
- and 9 to 12 weeks.

In the network-meta-analysis, clinical remission was stratified by extent of disease and separate NMAs were conducted for each clinically important follow-up time. To avoid duplication of study samples and to maximise data available, the final follow-up times assessed were:

- 0 to 2 weeks
- 0 to 4 weeks and
- 5 to 8 weeks.

Clinical evidence

Included studies

From the 2013 guideline, 34 randomised controlled trials (RCTs) were included, . Included in these are two secondary puplications (Connolly 2009 and Probert 2014) associated with one RCT (Marteau 2005). In November 2017, a systematic literature search, which was combined with NICE 'Crohn's disease: management' guideline update, was carried out to identify randomised controlled trials. From 9,811 articles, 50 were deemed relevant to the review protocol and retrieved in full. Of these, 15 new RCTs were included.

A top-up search in August 2018 found 20 potentially relevant articles from 1,350 articles. Of these, one RCT (Ogata 2018) was included.

In total, 50 RCTs, reported in 52 publications, were included.

See Appendix C for the search strategies and Appendix D for a PRISMA diagram summarising the process of study identification. See Appendix E: for a full list of references for the studies included in this review.

Excluded studies

From the 2013 guideline, there were 93 RCTs included. Of these, 34 RCTs were included in this guideline update and 59 were excluded. In this guideline update, from the 50 relevant articles identified, 35 articles were excluded. Additionally, 19 articles were excluded from the top-up search conducted in August 2018. For the excluded studies list with reasons for exclusion, please see Appendix M:. For references of excluded studies, please see Appendix E:

Summary of clinical studies included in the evidence review

Fifty RCTs, reported in 52 publications, were included.

- Seven RCTs compared standard-dose oral aminosalicylate with placebo:
  Dick 1964, Feurle 2013, Hanauer 1998; Hetzel 1986, Ito 2010; Pontes 2014 and Sninsky 1991.

- Three RCTs compared high-dose oral aminosalicylate with placebo:
  Feagan 2013; Scherl 2009 and Schroeder 1987.

- Three RCTs compared both standard-dose and high-dose oral aminosalicylate with placebo:
  Hanauer 1993, Kamm 2007 and Lichtenstein 2007.

- Eleven RCTs compared standard-dose aminosalicylates with high-dose aminosalicylates, according to the criteria outlined in Table 2.
  Dhaens 2006; Hanauer 2005, Hanauer 2007; Irvine 2008; Kruis 2003; Levine 2002; Ogata 2017; Ogata 2018; Pruit 2002; Sandborn 2009 and Suzuki 2016

- One RCT compared oral aminosalicylates with topical aminosalicylates:
  Gionchetti 1988

- Two RCTs compared oral corticosteroids with placebo:
  Rubin 2017 and Travis 2013.

- One RCT compared oral aminosalicylate, oral corticosteroid and placebo:
  Sandborn 2012.

- Three RCTs compared oral aminosalicylates with oral corticosteroids:
  Campieri 2003; Gross 2011; and LennardJones 1960.

- Five RCT compared topical aminosalicylates with placebo:
  Campieri 1990; Campieri 1990a; Campieri 1991; Poktrotnieks 2000 and Wantabe 2013.

- One RCTs compared topical aminosalicylates with topical corticosteroids:
  Lauritsen 1986.

- Four RCTs compared topical corticosteroids and placebo:
  Binder 1987; Naganuma 2016, Naganuma 2017 and Sandborn 2015.

- Two RCTs compared different preparations of topical corticosteroids:
  BarMier 2003 and Gross 2006.

- One RCT compared a combination of aminosalicylate and corticosteroid with placebo:
  Rizzello 2002.

- Two RCTs compared oral aminosalicylates with oral and topical aminosalicylates:
  Marteau 2005 (this study had 2 secondary publications: Connolly 2009 and Probert 2014) and Vecchi 2001.

- Two RCTs included a paediatric population:

Romano 2010 (high-dose aminosalicylate compared with beclomethasone) and Winter 2014 (compared high with standard dose high-dose aminosalicylate compared with standard-dose aminosalicylate).

- One RCT compared intravenous and subcutaneous methotrexate with placebo:
  Carbonnel 2016
  This RCT reported a minimum follow-up period of 24 weeks, and additional 12 week data was obtained from the authors via email.

- One RCT compared topical (ointment) tacrolimus and placebo:
  Lawrance 2017
  This RCT included an ointment preparation of tacrolimus and the committee noted that suppository tacrolimus is mostly used in the UK.

All RCTs including corticosteroids were deemed as standard dose. All topical preparations of aminosalicylates and corticosteroids were classed as standard dose.

No RCTs were included that reported on oral immunomodulators. Potentially relevant RCTs were identified from the 2012 iteration of this guideline, but were excluded as more than 10% of the population included in these studies had severe ulcerative colitis.

See Appendix F for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See the evidence tables in appendix F for quality assessment of individual studies and appendix H for full GRADE tables.

Economic evidence

Included studies

A literature search was conducted to identify published economic evaluations of relevance to the review question with a date limit of the previous 2013 guideline (Appendix C). The search returned 995 records, to which 4 studies identified in the previous guideline were added. Of the total 999 studies, 993 were excluded on the basis of title and abstract. The remaining studies were screened by reviewing the full text and 4 published studies were included in the review (Appendix J). The de novo economic model conducted in the 2013 guideline was reviewed in addition to the studies identified through the search of the published literature.

A top-up search in August 2018 identified 181 additional articles of which 180 were excluded on the basis of title and abstract.The remaining 1 study was excluded after reviewing the full text.

Excluded studies

Details of excluded studies are provided in Appendix M. For full referenes, see Appendix E:

Summary of studies included in the economic evidence review

The 4 published economic evaluations included in the review were limited to comparisons of different doses, formulations or combinations of mesalazine and are summarised in Table 3 with further details in Appendix K.

Buckland 2008

Buckland 2008 conducted a cost-utility analysis to compare 2.4g/day and 4.8g/day oral mesalazine for the induction of remission in patients with moderately active ulcerative colitis from a UK NHS perspective. The model was constructed as a decision tree with a 12-week time horizon. If remission was not achieved with mesalazine, patients were assumed to switch to oral steroids, followed by intravenous steroids, intravenous ciclosporin and then surgery. The probability of achieving remission on mesalazine was informed by a pooled analysis of 2 trials (ASCEND I/II) and assumed a treatment duration of 6 weeks regardless of the outcome. Health-state utility values were obtained from a multicentre study conducted in Spain (Casellas 2005), which reported significant correlation between EQ-5D scores and ulcerative colitis disease severity. Patients entering the model were assigned a utility of 0.50 to reflect moderate-severe disease and patients in remission were assigned a utility of 0.80. In addition to drug costs, the model captured hospital admission costs associated with intravenous adminsatration of steroids and ciclosporin. Disease-related outpatient costs and costs associated with surgery were obtained from a published single centre retrospective study of the cost of illness of inflammatory bowel disease in the UK (Bassi 2004).

In the base case deteriministic analysis, the 4.8g/day dose of mesalazine was found to be both more effective and less costly (dominant). Probabilistic sensitivity analysis indicated that the higher dose was cost effective in 72% of iterations at a threshold of £30,000/QALY. This study was deemed partially applicable as it only compared 2 different doses of oral mesalazine and did not include any other comparators of interest to the review question or model different sequences of treatments. The study was found to have potentially serious limitations in addressing the review question because the estimates of treatment effects for mesalazine were taken from a pooled analysis of only 2 studies, the downstream sequence of treatments for patients whose disease did not enter remission with mesalazine does not reflect current practice (no biologics were considered) and the source of funding for the study indicated a potential conflict of interest.

Connolly 2009

Connolly 2009 conducted a cost-utility analysis to compare 4g oral mesalazine in combination with 1g/100mL topical mesalazine enema with 4g oral mesalazine in combination with placebo enema taken daily for 8 weeks from a UK NHS perspective. The analysis was constructed as a Markov model with a time horizon of 32 weeks and consisted of 5 health states: active ulcerative colitis, mesalazine-refractory active ulcerative colitis, steroid-refractory active ulcerative colitis, infliximab-responsive active ulcerative colitis and remission. The probabilities of achieving remission with mesalazine were derived from a single RCT (Marteau 2005). Health-state utility values were obtained from a study by Poole 2008, which reported a value of 0.81 for active ulcerative colitis and 0.94 for remission measured using the EQ-5D. In addition to the cost of drugs, the model captured the costs of gastroenterologist and GP consultations and diagnostic examinations (blood tests, stool samples, sigmoidoscopy).

Table 3: Summary of economic evaluations included in the review

Study	Comparators	Incremental			Uncertainty	Applicability	Limitations
		Costs	Effects	Cost effectiveness			
Buckland 2008 (CUA)	INT 1: Oral mesalazine (2.4g/day)	£2,474	0.1378 QALYs	INT 2 dominates[a] INT 1	Results were sensitive to duration of mesalazine treatment; in PSA, probability that INT 2 is cost effective at a threshold of £30K/QALY is 72%	Partially applicable	Potentially serious limitations
	INT 2: Oral mesalazine (4.8g/day)	£2,382	0.1394 QALYs				
Connolly 2009 (CUA)	INT 1: Oral mesalazine (4g/day) + placebo enema	£2,388	0.55 QALYs	INT 2 dominates[a] INT 1	In PSA, INT 2 had a higher probability of being cost effective over threshold values from £0 - £20K/QALY	Partially applicable	Potentially serious limitations
	INT 2: Oral mesalazine (4g/day) + mesalazine enema (1g/100mL)	£1,813	0.56 QALYs				
Brereton 2010 (CUA)	INT 1: Oral mesalazine (2.4g/day)	£5,574	3.434 QALYs	ICER (INT 2 vs. INT 1): £749/QALY	In PSA, the probability that INT 2 is cost effective at a threshold of £20K/QALY is 74%	Partially applicable	Very serious limitations
	INT 2: Modified release multimatrix oral mesalazine (2.4g/day)	£5,582	3.445 QALYs				
Connolly 2014 (CUA)	INT 1: Oral mesalazine 2g oral twice daily	£2,978	0.56 QALYs	INT 2 dominates[a] INT 1	PSA was conducted varying remission rates only; only mean results reported	Partially applicable	Potentially serious limitations
	INT 2: Oral mesalazine 4g once daily	£2,600	0.57 QALYs				
2013 NICE Guideline (CUA)	INT 1: High-dose oral ASA, add topical ASA, prednisolone	£1,316	0.468 QALYs	ICER (INT 8 vs. INT 10): £42,622/QALY	In PSA, INT 10 had the highest probability of being cost effective at a threshold of £20K/QALY (54%)	Partially applicable	Minor limitations
	INT 2: High-dose oral ASA, prednisolone	£2,144	0.463 QALYs				

Study	Comparators	Incremental			Uncertainty	Applicability	Limitations
		Costs	Effects	Cost effectiveness			
	INT 3: Low-dose oral ASA, prednisolone	£2,345	0.458 QALYs	All other strategies are dominated			
	INT 4: Low-dose oral ASA, add topical ASA, prednisolone	£1,386	0.465 QALYs				
	INT 5: Low-dose oral ASA, high oral ASA, prednisolone	£1,509	0.459 QALYs				
	INT 6: Low-dose oral ASA, high oral ASA, add topical ASA, prednisolone	£1,013	0.461 QALYs				
	INT 7: High-dose oral ASA + topical ASA, prednisolone	£1,953	0.472 QALYs				
	INT 8: High-dose oral ASA + beclometasone, prednisolone	£1,364	0.481 QALYs				
	INT 9: Low-dose oral ASA, high oral ASA + beclometasone, prednisolone	£1,012	0.469 QALYs				
	INT 10: High-dose oral ASA, high oral ASA + beclometasone, prednisolone	£984	0.472 QALYs				

ASA = aminosalicylate; CUA = cost-utility analysis; QALY = quality-adjusted life year; PSA = probabilistic sensitivity analysis

(a) INT 2 is both more effective and less costly than INT 1

1

In the base case deterministic analysis, the combination treatment of oral and topical mesalazine was found to dominate. Probabilistic sensitivity analysis indicated that the combination treatment had the highest probability of being optimal over a range of threshold values from £0/QALY to £20,000/QALY. A scenario analysis was run restricting the time horizon to 16 weeks and excluding infliximab treatment; the combination of oral and topical mesalazine remained the dominant strategy. This study was deemed partially applicable as it only compared 2 different mesalazine treatment strategies and did not include any other comparators of interest to the review question or model different sequences of treatments. The study was found to have potentially serious limitations in addressing the review question because the estimates of treatment effects for mesalazine were taken from a single RCT and the source of funding for the study indicated a potential conflict of interest.

Brereton 2010

Brereton 2010 conducted a cost-utlity analysis to compare 2.4g/day oral mesalazine with 2.4g/day oral multimatrix (MMX) mesalazine from a UK NHS perspective. The analysis was constructed as a Markov model with a time horizon of 5 years and consisted of 8 health states: active disease with first-line mesalazine treatment, active disease with increased mesalazine dose (4.8g), active disease with second-line treatment (addition of oral corticosteroid), hospitalisation to receive immunosuppressant and/or intravenous steroids, surgery, post-surgery, remission and death. The probabilities of achieving remission with 2.4g/day mesalazine or MMX mesalazine were derived from a single RCT (Kamm 2007). Patients whose disease did not achieve remission at a dose of 2.4g/day were assumed to receive an increased dose of 4.8g/day mesalazine or MMX mesalazine. The model additionally assumed that patients whose disease was in remission would continue on mesalazine maintenance therapy. In scenario analyses, the model explored different assumptions about adherence to maintenance therapy and the impact of a lifetime time horizon taking the risk of developing colorectal cancer into account. Health-state utility values were obtained from a pooled analysis of 2 unpublished studies of 151 patients estimated using the EQ-5D and ranged from 0.317 for severe active disease to 0.845 for remission. In addition to the cost of drugs, the model captured the costs assocated with inpatient services, surgery and outpatient visits.

In the base case deterministic analysis, the incremental cost-effectivess ratio (ICER) for MMX mesalazine versus mesalazine was £749/QALY. Probabilistic sensitivity analysis indicated that MMX mesalazine had the highest probability of being optimal over threshold values from £0/QALY to £50,000/QALY. This study was deemed partially applicable as it only compared 2 mesalazine formulations and did not include any other comparators of interest to the review question or model different sequences of treatments. The study was found to have very serious limitations in addressing the review question because the estimates of treatment effects for mesalazine were taken from a single RCT, the downstream sequence of treatments for patients whose disease did not enter remission with mesalazine does not reflect current practice (no biologics were considered), additional uncertainty was introduced in the extrapolation of assumptions about maintenance treatment and the source of funding for the study indicated a potential conflict of interest.

Connolly 2014

Connolly 2014 conducted a cost-utility analysis to compare 2g oral mesalazine twice daily with 4g oral msealazine once daily. The analysis was constructed as a Markov model and consisted of 5 health states: active ulcerative colitis, mesalazine-refractory active ulcerative colitis, steroid-refractory active ulcerative colitis, infliximab-responsive active ulcerative colitis and remission. The model took the perspective of the Dutch healthcare system with a time horizon of 32 weeks. The probabilities of achieving remission with mesalazine were derived from a

single RCT (Flourié 2013). Health-state utility values were obtained from a study by Poole 2010, which reported a value of 0.78 for active ulcerative colitis and 0.84 for remission measured using the EQ-5D. In addition to the cost of drugs, the model captured the costs of gastroenterologist, GP and IBD nurse consultations and diagnostic examinations (laboratory tests, endoscopy, X-ray).

The authors concluded that 4g once daily mesalazine was more effective and less costly than 2g twice daily mesalazine. Only mean results of probabilistic sensitivity analysis were reported. This study was deemed partially applicable as it only compared 2 dosing schedules of oral mesalazine and did not include any other comparators of interest to the review question or model different sequences of treatments. The study was found to have potentially serious limitations in addressing the review question because the estimates of treatment effects for mesalazine were taken from a single RCT, results of probabilistic sensitivity analysis were not reported in full and the source of funding for the study indicated a potential conflict of interest.

2013 NICE guideline

The economic evaluations identified in the published literature were limited to comparisons of different doses, formulations or combinations of mesalazine and did not compare the full range of treatments or explore sequences of treatments of relevance to the review question. An original economic analysis was undertaken in the 2013 NICE guideline to evaluate the cost effectiveness of sequences of pharmacological treatments for the induction of remission of mild-to-moderate ulcerative colitis. The analysis was constructed as a decision tree with a time horizon of 28 weeks. The population entering the model was adults with mild-to-moderate left-sided or extensive ulcerative colitis defined as inflammation greater than 30-40cm. Other extents of disease were not modelled. The committee considered factors such as clinical practice, the suitability of drugs in patients with left-sided or extensive disease and the availability of RCT evidence to define 10 treatment sequences of interest for the cost-effectiveness model (Table 3). Up to 4 lines of treatment were modelled, followed by an assumption that patients whose disease did not respond to oral prednisolone would be hospitalised to receive intravenous steroids, intravenous ciclosporin or surgery.

A systematic review was conducted to identify RCTs that reported withdrawal due to adverse events and remission. Relative treatment effects for remission conditional on non-withdrawal were estimated in a network-meta-analysis. The baseline rates of withdrawal and remission were pooled from the placebo arms of the RCTs included in the systematic review. Health-state utility estimates were obtained from Poole 2010. In addition to the cost of drugs, the model captured costs assocated with inpatient treatment (intravenous therapy and surgery), blood tests, gastroenterologist, GP, specialist registrar and IBD nurse specialist consultations.

In the base-case analysis, treatment strategy #8 (high-dose oral aminosalicylate in combination with beclometasone in first line followed by oral prednisolone in seond line) was found to generate the most QALYs while treatment strategy #10 (high-dose oral aminosalicylate alone in first line followed by the addition of beclometasone in second line and then oral prednisolone in third line) was found to generate the lowest costs. The ICER for treatment strategy #8 versus #10 was £42,622/QALY. All other treatment strategies were dominated.

Since the 2013 guideline, a number of new comparators have entered the decision space and therefore the 2013 analysis was deemed only partially applicable to current practice. In addition, the analysis was categorised as having minor limitations because downstream clinical practice with respect the use of biologics in patients with moderately to severely active ulcerative colitis has evolved over time with the availability of NICE technology appraisal guidance on the use of Infliximab for acute exacerbations of ulcerative colitis guidance

(TA163), Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329) and Vedolizumab for treating moderately to severely active ulcerative colitis (TA342).

Economic model

Introduction

An economic analysis was undertaken in the 2013 guideline to evaluate the cost effectiveness of sequences of pharmacological treatments for the induction of remission of mild-to-moderate left-sided or extensive ulcerative colitis in adults. Since then, new RCTs were identified that would allow for additional drugs to be modelled as part of treatment sequences. In addition to the availability of new evidence, the committee wished to compare treatment sequences in all extents of disease and to update some of the assumptions underpinning the previous model to reflect current practice. Therefore, a decision was made to undertake a new cost-effectiveness analysis to compare sequences of pharmacological treatments for the induction of remission of mild-to-moderate ulcerative colitis drawing on the data from studies identified in the clinical evidence review. A summary of the methods and key findings of the economic model is provided below. A more detailed summary can be found in Appendix L.

Methods

The cost-effectiveness model was constructed as a decision tree and adopted a UK NHS/personal social services perspective with costs reported in GBP (£) and health outcomes reported as quality-adjusted life years (QALYs). The model only considered adults with mild-to-moderate ulcerative colitis because there was insufficient clinical evidence in young people and children to model sequences of treatments. The same model structure was used to run three separate analyses by extent of disease (proctitis, proctosigmoiditis and left-sided disease, extensive disease).

Clinically plausible treatment sequences were generated with input from the committee and after assessing the number of treatments and studies that were available to inform network meta-analyses at each time point and in each extent of disease. Although placebo was a common comparator in RCTs, the committee did not feel that ‘no treatment’ would be a clinically relevant comparator in the economic model. The analysis does not distinguish between people who are presenting with ulcerative colitis for the first time and those who are experiencing an inflammatory exacerbation. Some people may be receiving maintenance treatment such as an oral aminosalicylate prior to experiencing an inflammatory exacerbation and the committee advised that in clinical practice, people would likely continue this as the backbone of long-term treatment.

Treatment sequences contained up to 4 lines of treatment in proctitis and up to 3 lines of treatment in other extents of disease. In the model, if a person’s disease had not entered remission after 3 (or 4) lines of treatment, it was assumed that their disease had progressed to severe ulcerative colitis and they would receive rescue therapy in line with other NICE guidance. This included IV hydrocortisone as a first step, followed by IV ciclosporin, biological therapy or surgery. Surgery was assumed to be 100% effective in inducing remission so that by the end of the 30-week time horizon of the model, all patients’ disease would be in remission. Given the short time horizon, no discounting was applied to either costs or health outcomes.

Table 4 provides a description of the general treatment strategies (at the class level) by extent of disease. For each treatment strategy, multiple sequences were specified at the drug level for topical and oral corticosteroids, leading to a total of 32 treatment sequences in the cost-effectiveness anlaysis for proctitis, 75 in proctosigmoiditis and left-sided disease and 6 in extensive disease.

Table 4: Description of treatment strategies in the cost-effectiveness model by extent of disease

Proctitis			
1st line	**2nd line**	**3rd line**	**4th line**
Topical ASA	Add LD oral ASA	Topical CS	Topical tacrolimus
Topical ASA	Add LD oral ASA	Oral CS*	Topical tacrolimus
LD oral ASA	Add topical ASA	Topical CS*	Topical tacrolimus
LD oral ASA	Add topical ASA	Oral CS*	Topical tacrolimus
LD oral ASA + topical ASA	Topical CS*	Topical tacrolimus	-
LD oral ASA + topical ASA	Oral CS*	Topical tacrolimus	-
Topical ASA	Add LD oral ASA	Topical CS*	-
Topical ASA	Add LD oral ASA	Oral CS*	-
LD oral ASA	Add topical ASA	Topical CS*	-
LD oral ASA	Ad topical ASA	Oral CS*	-
LD oral ASA + topical ASA	Topical CS*	-	-
LD oral ASA + topical ASA	Oral CS*	-	-

Proctosigmoiditis and left-sided disease		
1st line	**2nd line**	**3rd line**
LD oral ASA	HD oral ASA	Oral CS*
LD oral ASA	HD oral ASA	Topical CS*
LD oral ASA	Add topical ASA	Oral CS*
LD oral ASA	Add topical ASA	Topical CS*
HD oral ASA	Add topical ASA	Oral CS*
HD oral ASA	Add topical ASA	Topical CS*
Topical ASA	Add LD oral ASA	Oral CS*
Topical ASA	Add LD oral ASA	Topical CS*
LD oral ASA + topical ASA	Oral CS*	-
LD oral ASA + topical ASA	Topical CS*	-
Topical CS	Add LD oral ASA	Oral CS*
Topical CS	Add HD oral ASA	Oral CS*
Topical CS	LD oral ASA + topical ASA	Oral CS*

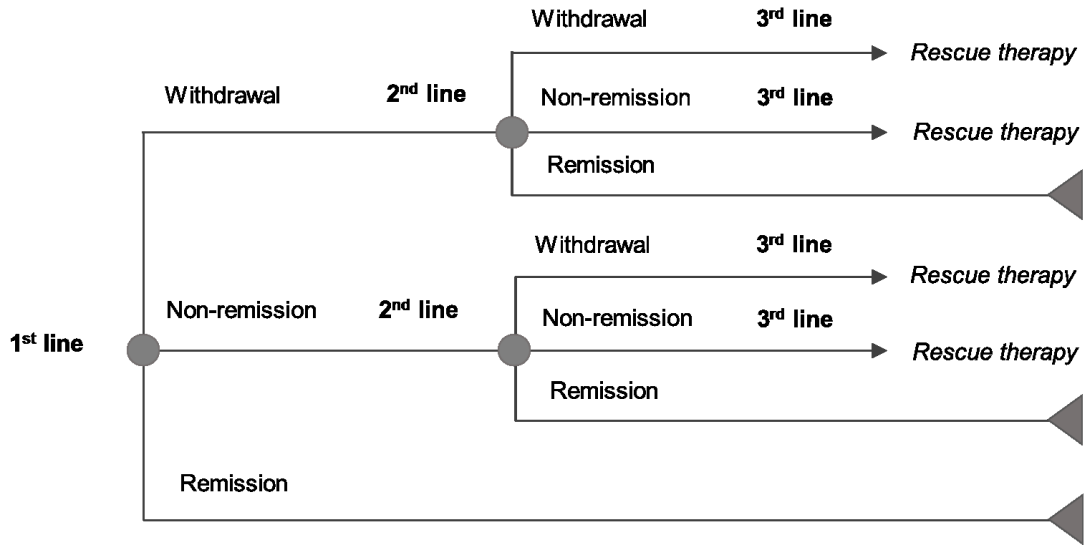
Extensive disease		
1st line	**2nd line**	**3rd line**
HD oral ASA	Add topical ASA	Oral CS*
HD oral ASA + topical ASA	Oral CS*	-

ASA = aminosalicylate; CS = corticosteroid; HD = high-dose; LD = low-dose
**Oral CS and topical CS are assumed to be given in addition to LD oral ASA unless a person has previously withdrawn from ASA treatment due to adverse events*

For each line of treatment, there are three possible mutually exclusive outcomes in the decision tree (Figure 1):

- Withdrawal from treatment due to adverse events; switch to next line of treatment
- Non-remission; switch to next line of treatment
- Remission.

Figure 1: Structure of the decision tree for a single sequence of treatments



In discussing duration of treatment, the committee noted that, for all drugs, response to treatment would generally be assessed earlier than the follow-up durations reported across RCTs so that, in the event of non-response, a decision could be made whether to switch to another drug. In order to reflect clinical practice, the model assumed that response to treatment is assessed halfway through a full course of treatment for the induction of remission, at which point people whose disease is not responding to treatment would move to the next line of treatment in the sequence. Therefore, for any given line of treatment, it was assumed that the duration of treatment for people in the non-remission branch of the decision tree was half that of people in the remission branch. The impact of this structural assumption on model results was explored in a scenario analysis in which no early switching of treatments was modelled; in other words all people except those withdrawing due to adverse events are assumed to complete a full course of treatment irrespective of whether the outcome was remission or non-remission. The base-case approach to the model structure has the advantage of reflecting clinical practice but the scenario analysis more closely reflects the clinical effectiveness evidence in relation to the design of the RCTs.

Model inputs for the probability of remission and withdrawal due to adverse events were obtained from the network meta-analyses presented in Appendix I. Drug costs were sourced from the online version of the British National Formulary (BNF). Estimates of health-state utility values for calculating QALYs and other healthcare resource use were sourced from published literature. Assumptions about treatment progression for severe ulcerative colitis in the hospital setting and on biological therapy were informed by data from the UK inflammatory bowel disease (IBD) national clinical audit of inpatient care (2014) and the UK IBD national clinical audit of biological therapies (2016).

Results

Proctitis: base-case analysis

Treatment sequences that begin with a topical aminosalicylate result in the highest proportion of people entering remission in first line (90.5%) and the lowest proportion of people requiring rescue therapy (0.1% - 3.0%). Table 5 shows the incremental cost-effectiveness results for the base-case analysis. The strategy PRC01 is associated with the highest probability of being cost effective and is both more effective and less costly than all other strategies except PRC17. The results also suggest that the use of topical tacrolimus as a fourth line treatment is cost effective but the absolute impact on total QALYs and total costs is small because the proportion of people requiring fourth-line treatment is very low.

Table 5: Base-case mean probabilistic cost-effectiveness results in proctitis

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[a]		
PRC01	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£448	0.5318				72.5%	£10,188
PRC03	tASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£459	0.5316	£11	-0.0001	dominated	18.4%	£10,174
PRC02	tASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£463	0.5312	£15	-0.0006	dominated	4.2%	£10,160
PRC04	tASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£486	0.5309	£38	-0.0008	dominated	0.0%	£10,133
PRC17	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£486	0.5319	£38	0.0001	£313,594	3.9%	£10,152
PRC19	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£514	0.5318	£27	-0.0001	dominated	0.5%	£10,123
PRC18	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£529	0.5314	£43	-0.0005	dominated	0.5%	£10,098
PRC20	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£578	0.5312	£92	-0.0007	dominated	0.0%	£10,047
PRC05	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£669	0.5178	£183	-0.0141	dominated	0.0%	£9,687
PRC09	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£699	0.5229	£213	-0.0090	dominated	0.0%	£9,758
PRC13	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£702	0.5227	£216	-0.0092	dominated	0.0%	£9,752
PRC07	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£712	0.5173	£226	-0.0146	dominated	0.0%	£9,633

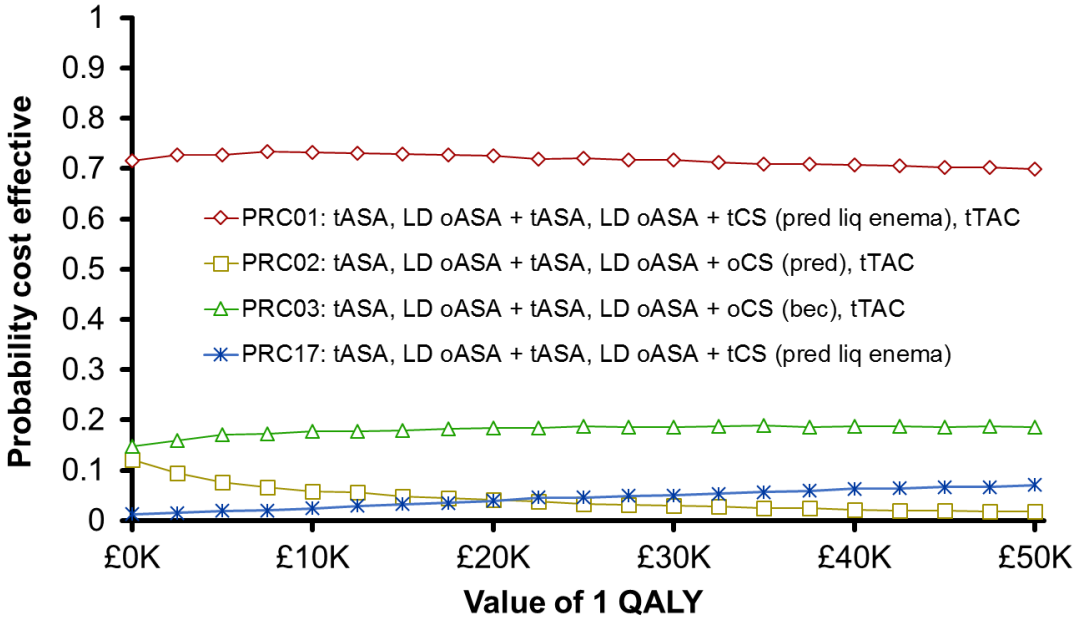
Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[a]		
PRC06	LD oASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£730	0.5152	£244	-0.0167	dominated	0.0%	£9,575
PRC11	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£769	0.5220	£283	-0.0099	dominated	0.0%	£9,671
PRC15	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£774	0.5218	£288	-0.0101	dominated	0.0%	£9,662
PRC10	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£800	0.5185	£314	-0.0134	dominated	0.0%	£9,570
PRC14	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£804	0.5183	£318	-0.0136	dominated	0.0%	£9,562
PRC08	LD oASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£818	0.5144	£332	-0.0175	dominated	0.0%	£9,470
PRC21	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£825	0.5183	£339	-0.0136	dominated	0.0%	£9,541
PRC23	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£935	0.5179	£449	-0.0140	dominated	0.0%	£9,424
PRC12	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£949	0.5171	£463	-0.0148	dominated	0.0%	£9,393
PRC16	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£956	0.5169	£469	-0.0150	dominated	0.0%	£9,382
PRC25	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£960	0.5236	£473	-0.0083	dominated	0.0%	£9,513
PRC29	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£966	0.5235	£480	-0.0084	dominated	0.0%	£9,504
PRC22	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,007	0.5160	£521	-0.0159	dominated	0.0%	£9,313
PRC27	LD oASA + tASA, LD oASA + oCS (beclo)	£1,141	0.5231	£655	-0.0088	dominated	0.0%	£9,322
PRC31	LD oASA + tASA, LD oASA + oCS (beclo)	£1,151	0.5229	£665	-0.0090	dominated	0.0%	£9,307
PRC24	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,203	0.5155	£717	-0.0164	dominated	0.0%	£9,107
PRC26	LD oASA + tASA, LD oASA + oCS (pred)	£1,264	0.5198	£778	-0.0121	dominated	0.0%	£9,132
PRC30	LD oASA + tASA, LD oASA + oCS (pred)	£1,275	0.5196	£789	-0.0123	dominated	0.0%	£9,117
PRC28	LD oASA + tASA, LD oASA + oCS (bude)	£1,597	0.5190	£1,111	-0.0129	dominated	0.0%	£8,782

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[a]		
PRC32	LD oASA + tASA, LD oASA + oCS (bude)	£1,613	0.5188	£1,127	-0.0131	dominated	0.0%	£8,763

PRC = proctitis; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; tTAC = topical tacrolimus; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

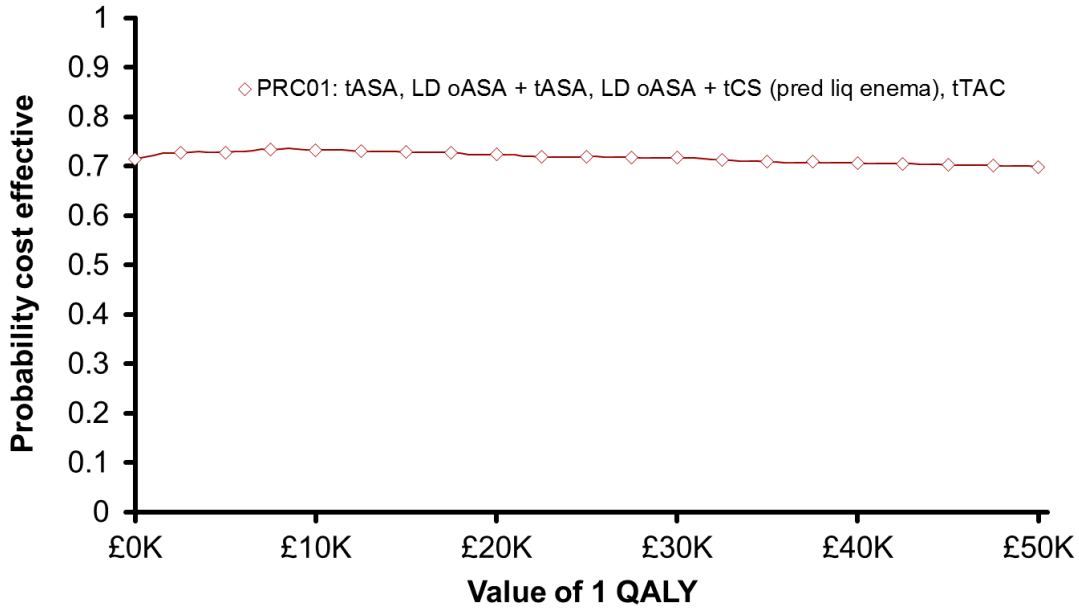
(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 2: Cost-effectiveness acceptability curve for proctitis base-case analysis



The cost-effectiveness acceptability curve shows all strategies with a >3% chance of being cost effective.

Figure 3: Cost-effectiveness acceptability frontier for proctitis base-case analysis



Proctitis: scenario analysis with no early switching of treatments in the event of non-remission

A scenario analysis was conducted in which the model did not allow for early assessment of response to treatment. All people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome is remission or non-remission. This scenario resulted in an increase in costs for all sequences but incremental cost-effectiveness results were consistent with the base-case analysis and PRC01 retained the highest probability of being cost effective over the range of threshold values from £0/QALY to £50,000/QALY. Full results for this scenario are presented in Appendix L.

Proctosigmoiditis and left-sided disease: base-case analysis

In proctosigmoiditis and left-sided disease, treatment sequences that begin with a topical aminosalicylate result in the highest proportion of people entering remission in first line (80.3%) and the lowest proportion of people requiring rescue therapy (3.1% - 7.6%). The incremental cost-effectiveness results are summarised in Table 6 along with expected net monetary benefit and the probability of each strategy being cost effective at a value of £20,000/QALY. At this threshold value, the strategy with the highest probability of being cost effective (PLS34) is not the the strategy with the highest expected net benefit (PLS31). This finding is further illustrated over a range of threshold values in the cost-effectiveness acceptability frontier (CEAF) in Figure 5, which plots the probability that the optimal option (as defined by expected net benefit) is cost effective. This result arises from asymmetry in the distributions of expected value (Fenwick 2001). Although there were more model iterations in which PLS34 generated a higher net benefit, in the iterations where PLS31 was superior, it was superior by a greater degree. The only difference between the sequences PLS31 and PLS34 is the mode of administration of the corticosteroid in the third line (oral prednisolone and topical prednisolone respectively).

Table 6: Base-case mean probabilistic cost-effectiveness results in proctosigmoiditis and left-sided disease

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[a]		
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£760	0.5283				14.5%	£9,806
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	£785	0.5263	£25	-0.0020	dominated	9.6%	£9,740
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£791	0.5291	£31	0.0008	£37,349	54.1%	£9,792
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	£794	0.5265	£3	-0.0026	dominated	5.4%	£9,737
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	£801	0.5259	£10	-0.0032	dominated	1.1%	£9,718
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£809	0.5291	£18	-0.0001	dominated	5.5%	£9,772
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (beclo)	£853	0.5273	£62	-0.0018	dominated	3.2%	£9,694
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (beclo)	£858	0.5275	£67	-0.0016	dominated	1.9%	£9,693
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (beclo)	£875	0.5271	£84	-0.0021	dominated	0.1%	£9,667
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£894	0.5280	£103	-0.0012	dominated	0.0%	£9,665
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	£969	0.5261	£178	-0.0030	dominated	0.0%	£9,553
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	£975	0.5258	£185	-0.0033	dominated	0.0%	£9,540
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	£1,011	0.5254	£220	-0.0037	dominated	0.0%	£9,497
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,050	0.5159	£259	-0.0132	dominated	0.0%	£9,268
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,064	0.5159	£273	-0.0132	dominated	0.0%	£9,254

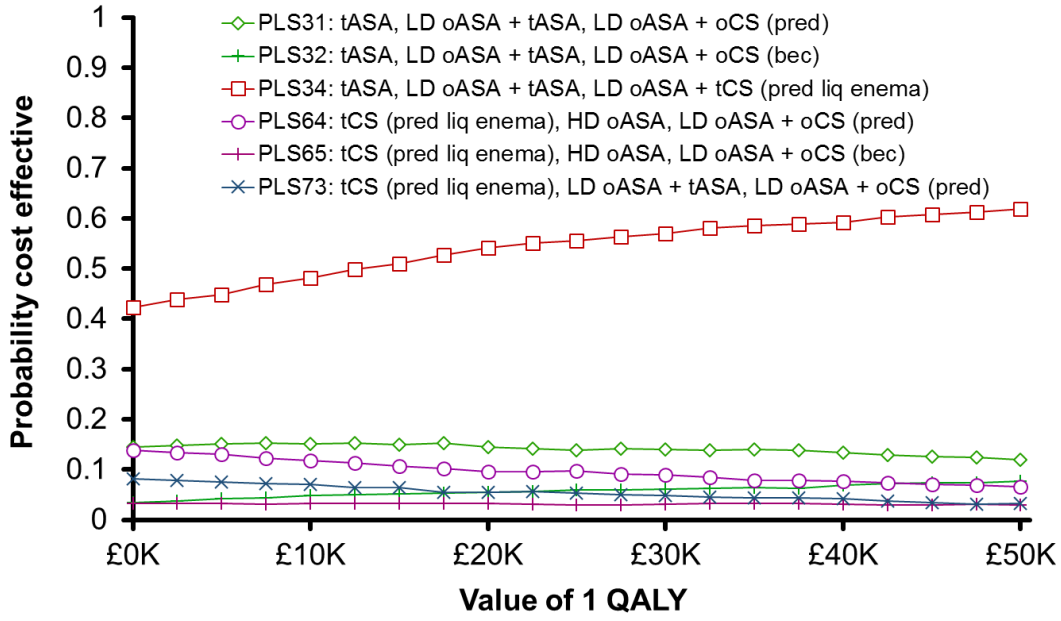
Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[a]		
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	£1,071	0.5172	£280	-0.0119	dominated	0.0%	£9,274
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,077	0.5162	£286	-0.0130	dominated	0.0%	£9,246
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	£1,078	0.5171	£287	-0.0121	dominated	0.0%	£9,264
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,091	0.5162	£300	-0.0130	dominated	0.0%	£9,232
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,173	0.5131	£383	-0.0160	dominated	1.8%	£9,089
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,188	0.5131	£397	-0.0160	dominated	0.0%	£9,074
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,189	0.5136	£398	-0.0155	dominated	0.8%	£9,083
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,203	0.5136	£412	-0.0156	dominated	0.0%	£9,068
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,265	0.5226	£474	-0.0065	dominated	0.0%	£9,187
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,270	0.5225	£479	-0.0066	dominated	0.0%	£9,180
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	£1,282	0.5166	£491	-0.0125	dominated	1.0%	£9,050
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,297	0.5151	£506	-0.0140	dominated	0.5%	£9,005
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,304	0.5154	£513	-0.0137	dominated	0.0%	£9,005
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,311	0.5151	£520	-0.0141	dominated	0.0%	£8,990
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,318	0.5154	£527	-0.0138	dominated	0.0%	£8,990
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	£1,430	0.5188	£639	-0.0103	dominated	0.1%	£8,947
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	£1,439	0.5186	£648	-0.0105	dominated	0.2%	£8,934
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	£1,470	0.5141	£679	-0.0150	dominated	0.0%	£8,813
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,517	0.5128	£726	-0.0164	dominated	0.0%	£8,738

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[(a)]		
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,527	0.5122	£736	-0.0169	dominated	0.0%	£8,718
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,533	0.5127	£742	-0.0164	dominated	0.0%	£8,722
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,543	0.5122	£752	-0.0169	dominated	0.0%	£8,701
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	£1,609	0.5216	£818	-0.0075	dominated	0.0%	£8,823
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	£1,621	0.5215	£830	-0.0076	dominated	0.2%	£8,809
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	£1,918	0.5176	£1,127	-0.0116	dominated	0.0%	£8,434
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	£1,932	0.5174	£1,141	-0.0118	dominated	0.0%	£8,416

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

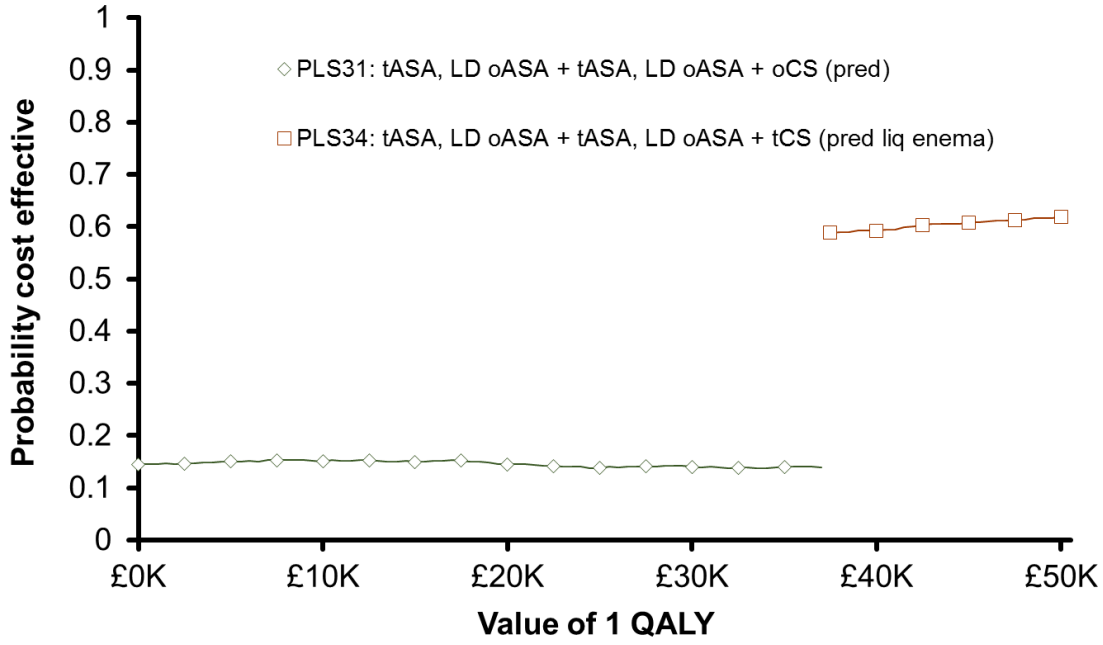
(a) *Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space*

Figure 4: Cost-effectiveness acceptability curve for proctosigmoiditis and left-sided disease base-case analysis



The cost-effectiveness acceptability curve shows all strategies with a >3% chance of being cost effective.

Figure 5: Cost-effectiveness acceptability frontier for proctosigmoiditis and left-sided disease base-case analysis



Proctosigmoiditis and left-sided disease: scenario analysis with no early switching of treatments in the event of non-remission

This scenario analysis assumes there is no early assessment of response to treatment. All people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome is remission or non-remission. Compared to the base case, there is an increase in costs for all sequences in this scenario and the ICER for PLS34 versus PLS31 has fallen to £20,340/ QALY. Full results for this scenario are presented in Appendix L.

Extensive disease: base-case analysis

In extensive disease, treatment sequences beginning with the combination of a high-dose oral aminosalicylate and a topical aminosalicylate result in a higher proportion of people entering remission in first line (68.3%) but also a higher proportion of people requiring rescue therapy (9.7% - 23.0%). This is beause it was only possible model up to two lines of treatment in the sequences that begin with the combination of a high-dose oral aminosalicylate and topical aminosalicylate. Although other potential treatment options may exist, no RCTs were identified for inclusion in the evidence network and so it was not possible to model a third line treatment in these sequences. This contributed to the high proportion of people progressing to rescue therapy in the economic analysis.

Table 7 summarises the base-case cost-effectiveness results in extensive disease. The sequence EXT05 (combination of high-dose oral aminosalicylate and a topical aminosalicylate in first line) results in an ICER of £34,091/QALY in comparison to EXT02 (high-dose oral aminosalicylate alone in first line followed by the addition of a topical aminosalicylate in second line if remission is not achieved).

Table 7: Base-case mean probabilistc cost-effectiveness results in extensive disease

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER[(a)]		
EXT02	HD oASA, HD oASA + tASA, LD oASA + oCS (beclo)	£888	0.5198				42.7%	£9,508
EXT03	HD oASA, HD oASA + tASA, LD oASA + oCS (pred)	£921	0.5186	£33	-0.0012	dominated	26.5%	£9,451
EXT05	HD oASA + tASA, LD oASA + oCS (beclo)	£1,060	0.5248	£172	0.0051	£34,091	22.9%	£9,436
EXT06	HD oASA + tASA, LD oASA + oCS (pred)	£1,118	0.5226	£58	-0.0022	dominated	7.7%	£9,335
EXT01	HD oASA, HD oASA + tASA, LD oASA + oCS (bude)	£1,125	0.5180	£65	-0.0068	dominated	0.2%	£9,236
EXT04	HD oASA + tASA, LD oASA + oCS (bude)	£1,495	0.5216	£435	-0.0032	dominated	0.0%	£8,937

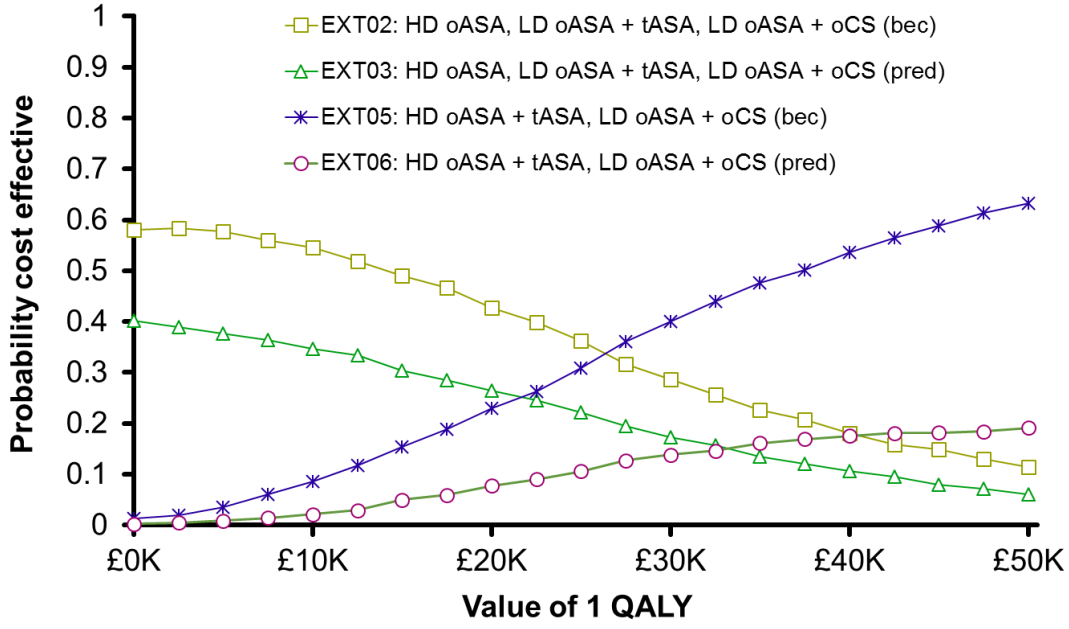
EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE =

Treatment sequence	Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
	Costs	QALYs	Costs	QALYs	ICER[a]		

cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

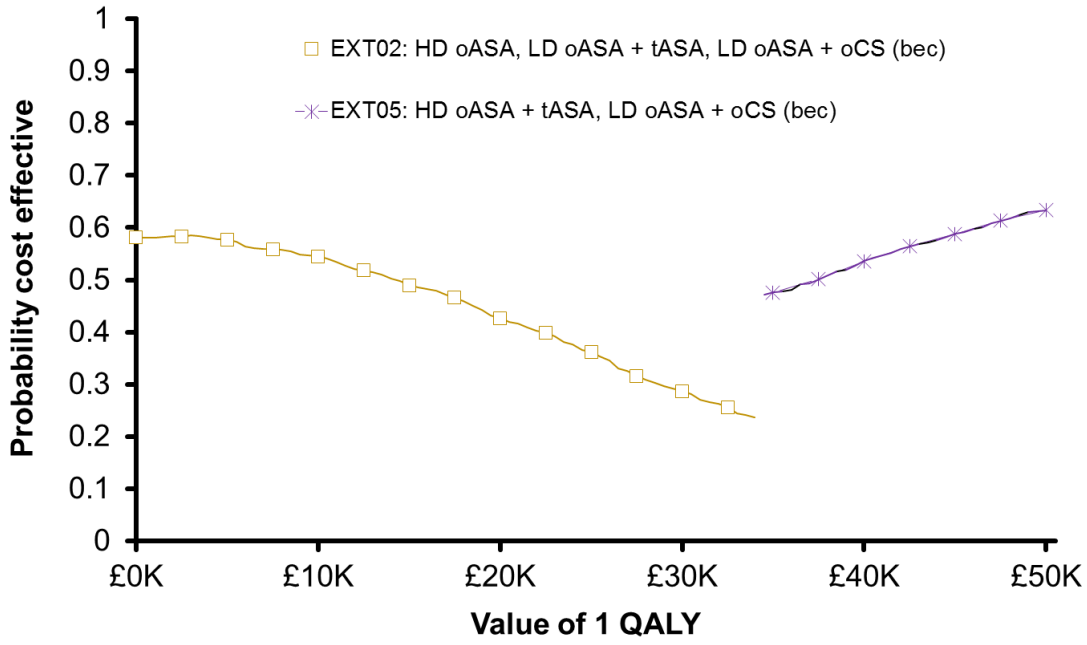
(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 6: Cost-effectiveness acceptability curve for extensive disease base-case analysis



The cost-effectivness acceptability curve shows all strategies with a >3% chance of being cost effective

Figure 7: Cost-effectiveness acceptability frontier for extensive disease base-case analysis



Extensive disease: scenario analysis scenario analysis with no early switching of treatments in the event of non-remission

A scenario analysis was run in which all people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome was remission or non-remission. This resulted in a reduction in the ICER for EXT05 versus EXT02 to £16,671/QALY.

Table 8: Mean probabilistic cost-effectiveness results for extensive disease with no early switching of treatments in the event of non-remission

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
EXT02	HD oASA, HD oASA + tASA, LD oASA + oCS (beclo)	£964	0.5106				20.8%	£9,248
EXT03	HD oASA, HD oASA + tASA, LD oASA + oCS (pred)	£1,014	0.5088	£50	-0.0018	dominated	11.3%	£9,162
EXT05	HD oASA + tASA, LD oASA + oCS (beclo)	£1,124	0.5202	£160	0.0096	£16,671	52.9%	£9,280
EXT06	HD oASA + tASA, LD oASA + oCS (pred)	£1,209	0.5170	£85	-0.0032	dominated	15.0%	£9,131
EXT01	HD oASA, HD oASA + tASA, LD oASA + oCS (bude)	£1,231	0.5075	£107	-0.0127	dominated	0.0%	£8,919

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
EXT04	HD oASA + tASA, LD oASA + oCS (bude)	£1,589	0.5147	£466	-0.0054	dominated	0.0%	£8,705

EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Evidence statements

Clinical evidence statements

Clinical evidence statements were based on results from network-meta-analyses, and where it was not possible to conduct a network-meta-analysis, the pairwise analyses was used. For full results of the pairwise analysis, see Appendix G: for forest plots and Appendix H: for GRADE tables.

Proctitis

Clinical remission in adults

0 to 2 weeks follow-up

Moderate quality evidence from 1 network-meta-analysis with 3 RCTs containing 214 participants found that topical aminosalicylates are associated with higher clinical remission than standard-dose oral aminosalicylates or placebo at 2 weeks follow-up. The evidence could not differentiate clinical remission between placebo and standard-dose oral aminosalicylates.

0 to 4 weeks follow-up

Moderate quality evidence from 1 network-meta-analysis with 4 RCTs containing 343 participants found that topical aminosalicylates are associated with higher clinical remission than placebo or standard-dose oral aminosalicylate at 3 to 4 weeks follow-up. The evidence could not differentiate clinical remission between placebo and standard-dose oral aminosalicylates.

5 to 8 weeks follow-up

Low quality evidence from 1 network-meta-analysis with 3 RCTs containing 279 participants found higher clinical remission in topical immunomodulators and standard-dose oral aminosalicylates than placebo at 5 to 8 weeks follow-up. The evidence could not differentiate clinical remission between topical aminosalicylates and:

- standard-dose oral aminosalicylates
- topical immunomodulators
- placebo

The evidence could not differentiate clinical remission between topical immunomodulators and standard-dose oral aminosalicylates.

Proctosigmoiditis and left-sided

Clinical remission in adults

0 to 2 weeks follow-up

Moderate quality evidence from 1 network-meta-analysis with 2 RCTs with 201 participants found that topical prednisolone or topical aminosalicylates are associated with higher clinical remission than placebo at 2 weeks follow-up. Topical aminosalicylates are associated with higher clinical remission than topical prednisolone, but 95% confidence intervals could not demonstrate a meaningful difference.

0 to 4 weeks follow-up

High quality evidence from 1 network-meta-analysis with 8 RCTs with 1,356 participants found that the following are associated with higher clinical remission at 0 to 4 weeks follow-up:

- topical corticosteroid (prednisolone) compared to placebo.
- topical aminosalicylates compared to placebo.
- standard-dose oral aminosalicylates combined with oral corticosteroid (beclomethasone) compared to oral corticosteroid (beclomethasone);
- standard-dose oral aminosalicylates combined with standard-dose oral corticosteroids (beclomethasone) compared to standard-dose oral aminosalicylates;

The following are associated with higher clinical remission, but 95% confidence intervals could not demonstrate a meaningful difference:

- topical aminosalicylates compared to oral corticosteroid (beclomethasone);
- high dose oral aminosalicylates compared to standard-dose oral aminosalicylates

The evidence could not differentiate clinical remission in the remaining interventions against each other or placebo.

5 to 8 weeks follow-up

Low quality evidence from 1 network-meta-analysis with 26 studies containing 6352 participants found that the following are associated with higher clinical remission compared to placebo at 5 to 8 weeks follow-up:

- topical aminosalicylates;
- standard-dose oral aminosalicylates;
- topical budesonide;
- topical hydrocortisone and
- high-dose oral aminosalicylates.

The following are associated with higher clinical remission at 5 to 8 weeks follow-up:

- oral budesonide compared to topical aminosalicylates

The following are associated with higher clinical remission, but 95% confidence intervals could not demonstrate a meaningful difference:

- oral budesonide compared to placebo;
- standard-dose oral aminosalicylates combined with topical aminosalicylates compared to placebo;
- oral budesonide compared to topical budesonide;
- oral budesonide compared to high-dose oral aminosalicylates;
- standard-dose oral aminosalicylates compared to topical aminosalicylates;

The evidence could not differentiate clinical remission in the remaining interventions against each other or placebo.

Quality of life

Very low quality evidence from 1 meta-analysis with 1 RCT containing 458 participants could not differentiate change in quality of life (IBD-QOL) between standard-dose oral corticosteroid and placebo from baseline to 8 weeks follow-up.

Moderate quality evidence 1 meta-analysis with 1 RCT containing 131 participants found an increase in change in quality of life (IBD-QOL) in high-dose topical aminosalicylates than standard-dose topical corticosteroids from baseline to 8 weeks follow-up.

Extensive

Clinical remission in children

Very low quality evidence from 1 RCT containing 81 participants could not differentiate clinical remission in standard-dose oral aminosalicylates and high-dose oral aminosalicylates (dose adjusted by body weight) at 6 weeks follow-up.

Clinical remission in adults

3 to 4 weeks follow-up

Low quality evidence from 1 network-meta-analysis with 3 studies containing 188 participants found higher clinical remission in high-dose oral aminosalicylates than l-standard-dose oral aminosalicylates at 3 to 4 weeks follow-up, but 95% confidence intervals could not demonstrate a meaningful difference.

The evidence could not differentiate clinical remission in the remaining interventions against each other or placebo.

5 to 8 weeks follow-up

Moderate quality evidence from 1 network-meta-analysis with 4 studies containing 331 participants found that the following are associated with higher clinical remission compared to placebo at 5 to 8 weeks follow-up:

- high-dose oral aminosalicylates and
- high-dose oral aminosalicylates combined with topical aminosalicylates.

The following are associated with higher clinical remission at 5 to 8 weeks follow-up:

- high-dose oral aminosalicylates combined with topical aminosalicylates compared to oral budesonide.

The following are associated with higher clinical remission, but 95% confidence intervals could not demonstrate a meaningful difference:

- high-dose oral aminosalicylates combined with topical aminosalicylates compared to high-dose oral aminosalicylates.

The evidence could not differentiate clinical remission between high-dose oral aminosalicylates and standard-dose oral corticosteroids.

12 weeks follow-up

Very low quality evidence from 1 RCT containing 111 participants found that methotrexate is associated with higher clinical remission at 12 weeks follow-up, but 95% confidence intervals could not demonstrate a meaningful difference.

Quality of life

Low quality evidence 1 meta-analysis with 1 RCT containing 127 participants could not differentiate change in quality of life (EQ-5D) between high-dose oral aminosalicylates and high-dose oral aminosalicylates combined with standard-dose topical aminosalicylates from baseline to 8 weeks follow-up.

All extents of disease

Withdrawal due to adverse events

Very low quality evidence from 1 network-meta-analysis with 28 studies containing 6,594 participants found higher withdrawal due to adverse events rates in high-dose oral aminosalicylates compared to the following:

- standard-dose oral corticosteroid
- topical corticosteroid
- placebo.

Higher withdrawal due to adverse events rates were found in standard-dose topical corticosteroid than standard-dose oral aminosalicylates.

The following are associated with higher clinical remission, but 95% confidence intervals could not demonstrate a meaningful difference:

- standard-dose oral aminosalicylates compared to high-dose oral aminosalicylates
- standard-dose topical corticosteroid compared to placebo

The evidence could not differentiate withdrawal due to adverse events the remaining interventions against each other or placebo.

Economic evidence statements

One partially applicable study with potentially serious limitations (Buckland 2008) compared 2.4g oral mesalazine with 4.8g oral mesalazine and taken daily for 8 weeks and found the higher dose was both more effective and less costly.

One partially applicable study with potentially serious limitations (Connolly 2009) compared 4g oral mesalazine in combination with 1g/100mL topical mesalazine enema with 4g oral mesalazine in combination with placebo enema taken daily for 8 weeks and found 4g oral mesalazine in combination with 1g/100mL topical mesalazine enema was both more effective and less costly.

One partially applicable study with very serious limitations (Brereton 2010) compared 2.4g oral mesalazine with 2.4g multimatrix oral mesalazine taken daily for 8 weeks. The study concluded that multimatrix mesalazine was cost effective with an ICER of £749/QALY compared to mesalazine.

One partially applicable study with potentially serious limitations (Connolly 2014) compared 2g oral mesalazine twice daily with 4g oral mesalazine once daily for 8 weeks and found that the once daily regimen was both more effective and less costly.

One partially applicable economic model with minor limitations from the 2013 guideline compared 10 sequences of treatments for the induction of remission of mild-to-moderate left-sided and extensive ulcerative colitis and concluded that the strategy of high-dose oral aminosalicylate in first line followed by the addition of beclomestaone in second line and oral prednisolone in third line was cost effective.

An original economic model was developed to compare 32 treatment sequences in proctitis, 75 treatment sequences in proctosigmoiditis and left-sided disease and 6 treatment sequences in extensive disease. In proctitis, proctosigmoiditis and left-sided disease, treatment sequences that start with a topical aminosalicylate, followed by the addition of an oral aminosalicylate and then either a topical or oral corticosteroid were found to be cost effective as they were more effective and less costly than other strategies. In extensive disease, there was more

uncertainty with respect to the optimal treatment sequence but results suggest that using a high-dose oral aminosalicylate in combination with a topical aminosalicylate in first line followed by an oral corticosteroid (in combination with an oral aminosalicylate) as second-line treatment is likely to be cost effective.

Recommendations

Proctitis

1 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctitis, offer a topical aminosalicylate[3] as first-line treatment

2 If remission is not achieved within 4 weeks, consider adding an oral aminosalicylate[4].

3 If further treatment is needed, consider adding a topical or oral corticosteroid[5].

4 For people who decline a topical aminosalicylate:

- consider an oral aminosalicylate as first-line treatment, and explain that this is not as effective as a topical aminosalicylate
- if remission is not achieved within 4 weeks, consider adding a topical or oral corticosteroid[5].

5 For people who cannot tolerate aminosalicylates, consider a topical or an oral corticosteroid.

Proctosigmoiditis and left-sided ulcerative colitis

6 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctosigmoiditis or left-sided ulcerative colitis, offer a topical aminosalicylate as first-line treatment.

7 If remission is not achieved, consider:

- adding a high-dose oral aminosalicylate to the topical aminosalicylate **or**
- switching to a high-dose oral aminosalicylate and a topical corticosteroid.

[3] At the time of publication (December 2018), some topical aminosalicylates did not have a UK marketing authorisation for this indication in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[4] At the time of publication (December 2018), some oral aminosalicylates did not have a UK marketing authorisation for this indication in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[5] At the time of publication (December 2018), beclometasone dipropionate only has a UK marketing authorisation 'as add-on therapy to 5-ASA containing drugs in patients who are non-responders to 5-ASA therapy in active phase'. Additionally, budesonide (oral or rectal) and prednisolone foam are not licensed in children. For use outside these licensed indications, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

8 If further treatment is needed, stop topical treatments and offer an oral corticosteroid and an oral aminosalicylate.

9 For people who decline any topical treatment:

- consider a high-dose oral aminosalicylate alone, and explain that this is not as as effective as a topical aminosalicylate
- if remission is not achieved, offer an oral corticosteroid in addition to the high-dose aminosalicylate.

10 For people who cannot tolerate aminosalicylates, consider a topical or oral corticosteroid.

Extensive disease

11 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of extensive ulcerative colitis, offer a topical aminosalicylate and a high-dose oral aminosalicylate as first-line treatment.

12 If remission is not achieved, stop the topical aminosalicylate and offer an oral corticosteroid[6] with a high-dose oral aminosalicylate.

13 For people who cannot tolerate aminosalicylates, consider an oral corticosteroid.

All extents of disease

1. For guidance on biologics for treating moderately to severely active ulcerative colitis, see the NICE technology appraisal guidance on:
   - infliximab, adalimumab and golimumab for moderately to severely active ulcerative colitis
   - vedolizumab for treating moderately to severely active ulcerative colitis.

Research recommendations

1. In mild-to-moderate first presentation or inflammatory exacerbation of proctitis that is resistant to standard treatment, what is the effectiveness of topical immunomodulators, such as tacrolimus, in achieving clinical remission and what is the most effective formulation (suppository/ointment)?

2. What is the effectiveness of oral tacrolimus and systemic (intramuscular/subcutaneous/oral) methotrexate in the induction of remission in mild-to-moderate UC unresponsive to aminosalicylates?

3. What is the clinical and cost effectiveness of oral prednisolone, budesonide, beclometasone in addition to aminosalicylates compared with each other and with

[6] licensing footnote for drugs available in adults only: oral prednisolone, oral budesonide, beclometasone.

aminosalicylate monotherapy for the induction of remission for people with mild-to-moderate ulcerative colitis?

Rationale and impact

Why the committee made the recommendations

Proctitis

The evidence showed that topical aminosalicylates (suppositories or enema) are the most effective treatments for achieving remission in people with mild-to-moderate proctitis, so these were recommended as first-line treatments. The evidence did not show any difference in effectiveness between enema and suppository.

Topical aminosalicylates alone are recommended for up to 4 weeks because the evidence showed that they were the most effective treatment within this timeframe. There was no direct evidence for combining topical and oral aminosalicylates for people with proctitis. However, evidence showed that this combination was effective for people with proctosigmoiditis, and the committee agreed that this evidence was also applicable to people with proctitis alone. The committee chose not to specify a dose for the oral aminosalicylate. It preferred to leave it open to clinical judgment depending on the specific situation (for example, the clinician could give a low dose if the person had not taken an aminosalicylate before, or a high dose if the person was already taking a low dose).

Some people will not achieve remission with topical and oral aminosalicylates. In clinical practice, oral or topical corticosteroids are commonly added at this stage, but there was no evidence on this combination. The committee agreed that, based on their experience, adding a topical or oral corticosteroid should be an option at this stage.

As the evidence showed that oral aminosalicylates are not as effective at inducing remission, the committee thought it was important to explain this to people who decline topical aminosalicylates. Despite no direct evidence for the effectiveness of topical or oral corticosteroids, the committee agreed that, based on their experience, these should be recommended to people who cannot tolerate aminosalicylates.

There was cost-effectiveness evidence showing that using an immunomodulator as the next line of treatment after oral or topical corticosteroids and oral aminosalicylate produced greater health benefits at lower total costs than other strategies. However, the clinical evidence on topical immunomodulators was limited and it was unclear how applicable it was to UK clinical practice. Because of this, the committee recommended the sequence without this final treatment, and recommended further research on topical immunomodulators.

Proctosigmoiditis or left-sided ulcerative colitis

There is evidence that topical aminosalicylates are effective for achieving remission in people with mild -to-moderate proctosigmoiditis or left-sided ulcerative colitis, so these are recommended as first-line treatment. Cost-effectiveness evidence showed that treatment sequences starting with topical aminosalicylates produced greater health benefits and incurred lower total costs than other strategies.

There is no direct evidence for the effectiveness of high-dose oral aminosalicylates combined with either topical aminosalicylates or topical corticosteroids. However, there is evidence that topical or high-dose oral aminosalicylates individually provide some benefit. Therefore, the committee agreed it was reasonable to recommend combinations of these if remission is not

achieved. While there was limited evidence for oral corticosteroids, in the committee's experience an oral corticosteroid may benefit people with proctosigmoiditis or left-sided disease if further treatment is needed. As a result, they recommended oral corticosteroids with oral aminosalicylates instead of topical treatment for these people. This reflects current practice for people who do not achieve remission with topical treatments and high-dose oral aminosalicylates.

In people who cannot tolerate aminosalicylates, topical or oral corticosteroids are recommended as they are also an effective treatment option.

Extensive ulcerative colitis

The evidence showed that people with mild-to-moderate extensive ulcerative colitis would benefit most from a combination of high-dose oral aminosalicylates with topical aminosalicylates as first-line treatment. There is evidence that an oral corticosteroid combined with a high-dose oral aminosalicylate is also effective, so the committee recommended this combination if remission is not achieved with aminosalicylates alone. In people who can not tolerate aminosalicylates, oral corticosteroids are recommended as they are also an effective treatment option.

The sequence of drugs recommended was more effective than starting with a high-dose oral aminosalicylate alone. There was some uncertainty around the cost effectiveness of this sequence. The data on the effectiveness of high-dose oral aminosalicylates combined with topical aminosalicylates was from an 8-week clinical trial. The committee believed that in practice, people whose disease did not respond to treatment within 4 weeks would switch to another treatment. When the cost-effectiveness analysis allowed for early switching, the combination of a high-dose oral aminosalicylate and topical aminosalicylate was not cost effective. However, if it was assumed that everyone continued treatment as described in the trial, the combination of a high-dose oral aminosalicylate and topical aminosalicylate was more likely to be cost effective. The committee agreed that although allowing for early switching was a better reflection of clinical practice, the other approach to the analysis more closely reflected the trial data.

The cost-effectiveness analysis found that starting with a combination of high-dose oral aminosalicylates with topical aminosalicylates then switching to an oral corticosteroid if remission is not achieved in 4 weeks was more effective than starting with a high-dose oral aminosalicylate alone but also more costly and not cost effective. The committee discussed the results of a sensitivity analysis in which people were assumed to remain on the combination of high-dose oral aminosalicylates with topical aminosalicylates for 8 weeks. This sensitivity analysis showed that one of the sequences that started with a combination of high-dose oral aminosalicylates with topical aminosaliyclates had the highest probability of being cost effective so the committee agreed to recommend a combination of high-dose oral aminosalicylates with topical aminosalicylates as first-line treatment.

There was some evidence on methotrexate for inducing remission, but it did not show a clear benefit. There was no evidence found on oral tacrolimus so the committee recommended further research to address the effectiveness of tacrolimus and methotrexate.

All extents of disease

There was limited evidence from paediatric populations, and the committee agreed that it is reasonable to generalise the recommendations made to all ages. There is limited evidence on oral corticosteroids. In addition, the committee agreed that the use of oral corticosteroid is generally reserved for later lines of treatment because of concerns about side effects. It is not

clear which corticosteroid is most effective for each extent of disease. There is also limited evidence on immunomodulators, specifically oral tacrolimus and systemic methotrexate for each extent of disease. The committee recommended further research to address these uncertainties

Impact of the recommendations on practice

The new recommendations classify the extents of ulcerative colitis differently. This will be clearer and more informative for people with mild–to-moderate ulcerative colitis and healthcare professionals. It more closely reflects current practice.

The recommendations in the 2013 guideline referred to specific corticosteroids. To better reflect the available evidence, the updated recommendations refer to corticosteroids as a class rather than recommending individual corticosteroids. This allows healthcare professionals and people with mild-to-moderate ulcerative colitis to choose the most appropriate corticosteroid, depending on patient preference, availability and acquisition cost.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes for decision making were clinical remission, withdrawal due to adverse events and quality of life. No other outcomes were included in the evidence review. The committee agreed that it was sensible to stratify the evidence and recommendations based on extent of disease: proctitis; proctosigmoiditis and left-sided; extensive ulcerative colitis. It also agreed specific follow-up times that are clinically important, including 2 weeks, 3 to 4 weeks, 5 to 8 weeks and 9 to 12 weeks. These follow up times were suggested because they represented points by which the committee agreed some clinical change would be expected.

Evidence for clinical remission and withdrawal due to adverse events in different extents of disease at the specified follow-up times were analysed in network meta-analyses. There was limited evidence for quality of life, all of which used different questionnaires including IBDQ, IBD-QOL and EQ-5D. Due to the limited evidence and the use of different questionnaires, evidence for quality of life could not be analysed in a network meta-analysis, but was presented to the committee in pairwise analyses (appendix G and appendix H).

The quality of the evidence

The majority of the evidence in the RCTs included a population with mild-to-moderate ulcerative colitis but there was insufficient evidence to stratify results by mild and moderate ulcerative colitis separately. The dates of the studies included ranged from 1960 to 2017 and the committee noted that older studies may be less applicable to current practice. This is because drug licensing, clinical knowledge on the effectiveness of different drugs and clinical practice has evolved in the last few decades. In spite of this, the committee agreed that the evidence provided by the older studies remained useful and therefore it was included in the analysis.

The committee noted that clinical remission was reported differently between RCTs. While some report 'clinical remission', some use the terms 'remission' or 'symptomatic remission'. The committee agreed that it was safe to assume that these outcomes are the same as clinical remission and therefore the studies were not downgraded for indirectness. The committee noted that some RCTs report 'clinical response' and/or 'clinical improvement' and that these outcomes were different from clinical remission. Therefore, these outcomes were not included in this guideline update.

The committee noted that the evidence from one RCT (Lawrance 2017) of 20 participants which compared tacrolimus and placebo in people with procitis was of low quality and may not be directly appropriate to a UK population. This is because the tacrolimus preparation used in the RCT was an ointment applied internally, while the committee agreed that in clinical practice, the most common form of tacrolimus applied topically would be suppositories. The RCT specified that the population included contained moderate to severe ulcerative colitis, but as the mean severity score was moderate, the committee agreed that the population is applicable to the evidence review. The RCT provided evidence for clinical remission at 5 to 8 weeks follow-up, but due to the low sample size and no clinical remission in the placebo arm, the RCT contributed to heterogeneous results in the network-meta-analysis. A sensitivity analysis analysis of clinical remission at 5 to 8 weeks remission which excluded this RCT was carried out. The results of this analysis showed that standard-dose oral aminosalicylates have the highest probability of being the best treatment option, while topical aminosalicylates and placebo are second and third best treatment options. The committee agreed not to recommend topical tacrolimus or other topical immunomodulators without better evidence and wrote a research recommendation to examine the effectiveness of topical immunomodulators in achieving clinical remission in first presentation or inflammatory exacerbation of proctitis that is resistant to standard treatment. Additionally, the committee noted that it is unclear which formulation of topical immunomodulator (suppository or ointment) is more clinically effective in practice and this was included in the research recommendation.

Benefits and harms

The committee noted the importance of stratifying evidence for standard and high-dose oral aminosalicylates, as doses prescribed for induction of remission in mild-to-moderate ulcerative colitis vary in clinical practice. The committee noted that there was evidence for oral corticosteroids which were above the doses specified for induction of remission in the British National Formulary (BNF). The committee agreed that in their experience, doses of oral prednisolone above 40mg per day would not be given in clinical practice due to possible adverse events. Additionally, one RCT (Rizzello 2001) included 10mg oral beclomethasone. The committee agreed that in their experience, doses above 5mg per day of oral beclomethasone would not be given in clinical practice. Therefore, these doses were not included in the final network-meta-analysis and all oral doses of steroids were considered as standard dose.

The committee noted that all RCTs including topical preparations of aminosalicylates or corticosteroids included doses within the range specified in the BNF for induction of remission, apart from one RCT (Naganuma 2016) which included budesonide 2mg foam given twice a day. The committee agreed it was suitable to treat this as standard dose, as the committee believed there is no dose effect with increased doses of topical preparations.

Proctitis

The committee reviewed the results from the network-meta-analysis for clinical remission at 2, 3 to 4 and 5 to 8 weeks follow-up. The committee noted that at both 2 weeks and 3 to 4 weeks

follow-up, topical aminosalicylates (either suppository or enema) have the highest probability of being the best treatment to achieve clinical remission. The committee also noted that the network meta-analysis for withdrawal due to adverse events in proctitis showed that topical aminosalicylates have lower withdrawal rates than standard-dose oral aminosalicylates and oral corticosteroids alone, which could be because oral treatments alone are not as effective as topical treatment, and this can lead to worsening of symptoms. The committee agreed that the evidence was reflective of clinical practice, as topical aminosalicylates would be considered as first-line treatment and formulated an 'offer' recommendation to reflect this. The committee did not specify which preparation of topical aminosalicylate, for example, suppository or enema, as the evidence found no difference in clinical remission according to different preparations and the committee agreed either can be used in accordance with the person's preference.

Evidence was not available in proctitis for combined treatment of topical and oral aminosalicylates. However, the committee reviewed the health economic model, which used evidence of combined treatment from proctosigmoiditis and left-sided ulcerative colitis, and noted that it would be of clinical benefit to add oral aminosalicylates as a second-line therapy if remission is not achieved within 4 weeks. Due to lack of clinical evidence for this, the committee formulated a 'consider' recommendation.

The committee discussed treatment options for people whose disease had not entered remission after combination treatment with both a topical and oral aminosalicylate. The evidence showed similar effectiveness and costs to support the use of either a topical or oral corticosteroid with an oral aminosalicylate as a next step in the treatment sequence. In the cost-effectiveness model, upon the advice of the committee, it was assumed that the corticosteroid would be given in addition to continuing treatment with an oral aminosalicylate. The committee also discussed that in clinical practice, a topical or oral corticosteroid may be given in addition to continuing treatment with both a topical and oral aminosalicylate. In other words, the committee felt that some people requiring third-line treatment for proctitis could benefit from receiving a triple combination of a topical corticosteroid plus topical aminosalicylate plus oral aminsalicylate or of an oral corticosteroid plus topical aminosalicylate plus oral aminosalicylate. No RCTs were identified that provided evidence of either the effectiveness or frequency of withdrawals for these triple combinations nor were they explicitly modelled in the cost-effectiveness analysis. Therefore, the committee made a consensus-based recommendation to allow all three treatments to be considered for use in combination in third-line treatment for proctitis. The committee noted that some people decline topical aminsalcylates. In these situations, the committee recommended that oral aminosalicylates can be considered as first-line treatment. However, the clinical evidence and the committee's experience show that oral aminosalicylates are not as effective for inducing remission as topical aminosaicylates alone. The committee highlighted in the recommendation that this difference in effectiveness in oral aminosalicylates alone should be explained to the person declining topical treatment. The committee recommended to consider adding a topical or oral corticosteroid if remission is not achieved within 4 weeks in these people. As there was no direct evidence for people who decline topical aminosalicylates and recommendations were derived from the health economic model and the committee's experience; 'consider' recommendations were made for these people.

The committee noted that there are people who do not tolerate aminosalicylates. The committee recommended to consider a topical or oral corticosteroid to these people.

Proctosigmoiditis and left-sided

The committee noted that evidence from the network-meta-analyses of clinical remission at 2 weeks, 3 to 4 weeks and 5 to 8 weeks follow-up showed that both topical aminosalicylates and

topical corticosteroids are effective in inducing clinical remission. Additionally, the evidence does not make a clear distinction between topical aminosalicylates and topical corticosteroids. The committee noted that, in its experience, topical aminosalicylates may work faster and more effectively than topical corticosteroids and recommended offering topical aminosalicylates as a first-line treatment for mild-to-moderate proctosigmoiditis or left-sided ulcerative colitis.

In addition to evidence of clinical effectiveness of topical corticosteroids, the committee noted that evidence from the network-meta-analysis at 3 to 4 weeks and 5 to 8 weeks follow-up showed that high-dose oral aminosalicylates are effective in inducing remission and reducing withdrawal due to adverse events and showed some benefit over standard-dose oral aminosalicylates. The committee noted that despite lack of direct evidence of high-dose oral aminosalicylates in combination with topical aminosalicylates or topical corticosteroids, it is possible to infer that as topical treatments are effective and high-dose oral aminosalicylates are more effective than standard-dose, then combination treatment of high-dose oral aminosalicylates with topical aminosalicylates or topical corticosteroids would be more effective than standard-dose oral aminosalicylates alone. The committee recommended considering adding high-dose oral aminosalicylates to the topical aminosalicylate or switching to high-dose oral aminosalicylates and topical corticosteroids if remission is not achieved.

The committee noted that there was limited evidence of oral corticosteroids available in proctosigmoiditis and left-sided disease. There was evidence from the network-meta-analysis at 5 to 8 weeks follow-up to suggest that oral corticosteroids are associated with higher clinical remission than placebo. However, the committee noted that this evidence is from one RCT which included budesonide. At 3 to 4 weeks, the network-meta-analysis could not differentiate clinical remission between oral corticosteroids and placebo, and this evidence was from one RCT which included beclomethasone. The committee discussed this and noted that in clinical practice, oral prednisolone would be the preferred choice of oral corticosteroids due to its established use in clinical care and lower acquisition cost. Despite the limited evidence, the committee recognised that there may be a benefit to offer an oral corticosteroid with an oral aminosalicylate if further treatment is needed.

The committee recommended that in situations where a person declines topical treatment a high-dose oral aminosalicylates alone could be considered, but that it is important to to explain to the person that this treatment is not as effective as a topical aminosalicylate. For these people, if remission is not achieved, the committee recommended that they be offered an oral corticosteroid in addition to the high-dose aminosalicylate.

The committee noted that there are people who do not tolerate topical aminosalicylates. The committee recommended to consider a topical or oral corticosteroid to these people.

Extensive disease

No evidence was found that reported clinical remission at 2 weeks follow-up in extensive disease. The committee noted that this may be consistent with clinical practice as extensive ulcerative colitis may require a longer duration of treatment compared with proctitis, proctosigmoiditis and left-sided disease. To allow the network to become connected, the option of using the relative effectiveness of clinical remission in high-dose compared to standard-dose oral aminosalicylates in proctosigmoiditis and left-sided disease was discussed with the committee. The committee agreed that it would be suitable to assume that the relative effectiveness of this comparison in proctosigmoiditis and left-sided extent of disease would be comparable in extensive disease. Additionally, this was the only circumstance where evidence from two different corticosteroids (beclomethasone or prednisolone) were available. The committee agreed that as the clinical use, availability and cost of these different corticosteroids differs, it would be useful to stratify the corticosteroid drugs rather than combine into a class.

The results of this network-meta-analysis found that either oral beclomethasone or prednisolone and high-dose oral aminosalicylate in combination with a topical aminosalicylate are the best treatment options in achieving clinical remission. Evidence of clinical remission at 5 to 8 weeks follow-up was analysed in a network-meta-analysis and found that high-dose oral aminosalicylate in combination with a topical aminosalicylate has the highest probability of being the best treatment option in achieving clinical remission. The second and third best treatment options were high-dose oral aminosalicylate and oral budesonide respectively.

The committee discussed oral beclometasone and agreed that it is not widely used in clinical practice and from their experience, the preference among people with extensive ulcerative colitis was to use other oral corticosteroids. The committee noted that oral prednisolone is most widely used, but evidence of oral prednisolone in the analysis was from one dated RCT (Lennard Jones 1960) with a small sample size (20 participants). Due to this evidence from a low-quality RCT, the committee agreed that there is still uncertainty about the effectiveness of oral prednisolone and oral corticosteroids as first line treatment in extensive disease. The committee felt that due to this uncertainty, it would not be suitable to recommended oral corticosteroids as first-line treatment for extensive disease, but recommended offering a combination of oral high-dose aminosalicylates with a topical aminosalicylate as first-line treatment. However, the committee recommended that if first-line treatment does not achieve clinical remission, an oral corticosteroid with a high-dose oral aminosalicylate can be offered. The committee noted that there are people who do not tolerate topical aminosalicylates. The committee recommended to consider oral corticosteroid to these people.

The committee noted that for all extents of disease, it would be reasonable to assume that the evidence found for the adult population would be comparable to paediatric population, as the same treatment options would be considered in clinical practice. The committee decided to generalise the recommendations made to include children, young people and adults, but to include a footnote to clarify that oral prednisolone, budesonide and beclomethasone are not licensed for use in children with ulcerative colitis if these are considered as second-line treatment options.

The committee reviewed evidence for clinical remission and withdrawal due to adverse events at 12 weeks follow-up received from the authors of one RCT (Carbonnel 2016) which compared methotrexate and placebo. This was the only evidence included for extensive ulcerative colitis which for a follow-up of greater than 8 weeks and was analysed in a pairwise meta-analysis. This evidence did not show a meaningful difference of a benefit of methotrexate at the 95% confidence interval. The committee believe that evidence on the effectiveness of methotrexate is lacking and evidence on this would benefit future guidance for the induction of remission. The committee formulated a research recommendation to examine the effectiveness of systemic methotrexate (and also oral tacrolimus) in the induction of remission in mild-to-moderate ulcerative colitis.

Cost effectiveness and resource use

A review of the published literature identified 4 cost-effectiveness analyses that compared different doses or formulations of mesalazine for the induction of remission in mild-to-moderate ulcerative colitis. None of these studies provided information on the comparative cost effectiveness of different sequences of treatments. In order to address this gap in the evidence, a cost-effectiveness model was developed as part of the 2013 guideline. It compared 10 sequences of treatments for the induction of remission of mild-to-moderate left-sided or extensive ulcerative colitis in adults. Since then, new RCTs have been published that provide data to compare additional treatment sequences. The committee also wished to explore the

cost effectiveness of treatment sequences in different extents of disease and to update some of the assumptions underpinning the 2013 guideline model to reflect current practice. Therefore, a new economic model was developed to take these considerations into account.

The results of the model showed that in proctitis as well as in proctosigmoiditis and left-sided disease, treatment sequences that begin with a topical aminosalicylate, followed by the addition of a standard-dose oral aminosalicylate and then a topical or oral corticosteroid resulted in the highest proportion of people achieving remission in first line and the lowest proportion of people requiring rescue therapy. These sequences also generated the highest total QALYs and the lowest total costs. The differences in total QALYs between sequences that started with a topical aminosalicylate were very small and the committee felt there was not a strong basis for differentiating between treatment strategies in terms of the choice of corticosteroid in third line. The committee acknowledged the limited evidence base for corticosteroids in proctitis and proctosigmoiditis and left-sided disease. For example, there were no studies that compared oral prednisolone in either extent of disease. In addition, given the available evidence, it was not possible to directly establish whether a class-level effect could also be applied to corticosteroids, because for both oral corticosteroids and topical corticosteroids, the individual drugs within the class were not all connected in a common network. The committee noted that although there were differences in the weekly cost of varous topical and oral corticosteroid preparations, the sequencing model was somewhat insensitive to these differences because of the diminishing proportion of people who required subsequent lines of treatment and the relatively low cost of corticosteroids in comparison to the costs associated with rescue therapy.

In proctitis, treatment sequences were modelled both with and without topical tacrolimus as a fourth-line treatment option. The committee noted that the clinical evidence to inform the remission rate for topical tacrolimus was based on 1 RCT of 20 participants (Lawrance 2017) and that the preparation used in the trial did not reflect UK clinical practice. Given this uncertainty and the pharmacy costs associated with compounding tacrolimus suppositories on a case by case basis, the committee decided not to recommend topical tacrolimus as part of the treatment sequence in proctitis and agreed instead to make a research recommendation.

In proctosigmoiditis and left-sided disese, the committee discussed whether the dose of the oral aminosalicylate in second line should be standard or high. Based on the available RCT evidence in proctosigmoiditis and left-sided disease, it was only possible to model standard-dose oral aminosalicylates in combination with a topical aminosalicylate as part of treatment sequences in the economic model. However, the committee noted the superior efficacy of high-dose oral aminosalicylates in comparison to standard-dose oral aminosalicylates when used alone and inferred that the superior efficacy of high-dose oral aminosalicylates was likely to hold when used in combination with a topical aminosalicylate. The committee also noted that in clinical practice, a high-dose oral aminosalicylate is more likely to be used in people who have not responded to a topical aminosalicylate alone.

In extensive disease, treatment sequences that begin with a combination of a high-dose oral aminosalicylate and a topical aminosalicylate resulted in a higher proportion of people achieving remission in first line compared to a high-dose oral aminosalicylate alone but also resulted in a higher proportion of people requiring rescue therapy. In the base-case analysis, the ICER for EXT05 (high-dose oral aminosalicylate in combination with a topical aminosalicylate in first line followed by oral beclometasone in second line) versus EXT02 (high-dose oral aminosalicylate in first line followed by the addition of a topical aminosalicylate in second line and then oral beclometasone in third line) was £34,091/QALY; this fell to £16,671/QALY in a scenario analysis in which all people, except those withdrawing due to adverse events, were assumed to complete a full course treatment irrespective of whether the

outcome was remission or non-remission. It was noted that in treatment sequences that begin with a high-dose oral aminosalicylate in combination with a topical aminosalicylate, it was only possible to model two lines of treatment as no RCT evidence was identified to model a third line treatment in extensive disease. In practice, the availability of other treatment options in third line would likely further reduce the proportion of people requiring rescue therapy, leading to lower costs and reducing the ICER.

Overall, the committee felt that the recommendations would not have a significant resource impact because they are generally in line with clinical practice for all extents of disease.

Other factors the committee took into account

The committee noted that topical tacrolimus, mainly suppositories, are occasionally used in clinical practice for people with proctitis. However, evidence on topical tacrolimus in people with proctitis is limited. The committee formulated a research recommendation to examine the clinical and cost-effectiveness of topical tacrolimus compared with topical aminosalicylates in the induction of remission.

The committee recognised the limited evidence base for oral corticosteroids and the uncertainty over which oral corticosteroid is most clinically and cost effective in all extents of disease, but in particular for proctosigmoiditis, left-sided and extensive disease. The committee formulated a research recommendation to examine the clinical and cost effectiveness of prednisolone, budesonide and beclomethasone in addition to aminosalicylates compared with each other for the induction of remission in people with mild-to-moderate ulcerative colitis.

Appendix A: Review protocol for induction of remission in mild-to-moderate ulcerative colitis

Review protocol for induction of remission in mild-to-moderate ulcerative colitis

<table>
<tr><th>ID</th><th>Field (based on PRISMA-P)</th><th>Content</th></tr>
<tr><td>I</td><td>Review question</td><td>In adults, children and young people with mild-to-moderate ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates, immunomodulators (methotrexate, mycophenolate and tacrolimus) for the induction of remission compared to themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?</td></tr>
<tr><td>II</td><td>Type of review question</td><td>Intervention</td></tr>
<tr><td>III</td><td>Objective of the review</td><td>To update and expand the question in CG166. To assess the clinical and cost effectiveness of corticosteroids, aminosalicylates, immunomodulators and other relevant drugs vs. placebo, themselves and each other for the induction of remission in ulcerative colitis and to develop a recommended sequence strategy for drug treatment in induction of remission in ulcerative colitis.</td></tr>
<tr><td>IV</td><td>Eligibility criteria – population</td><td>Included: Children young people and adults (18 years and older), with a diagnosis of mild-to-moderate (author defined) ulcerative colitis.

Excluded: Mixed IBD populations where the results are not displayed separately for ulcerative colitis. People with indeterminate or idiopathic colitis. Chronic active ulcerative colitis. Inflammatory bowel disease-undefined (IBD-U) and colitis. Greater than 10% of the study population has severe ulcerative colitis.</td></tr>
<tr><td>V</td><td>Interventions</td><td>
<table>
<tr><td rowspan="2">Corticosteroids</td><td>Prednisolone
(alone only when Aminosalicylates not tolerated)</td></tr>
<tr><td>Hydrocortisone</td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>Budesonide
(alone only when Aminosalicylates not tolerated)</td></tr>
<tr><td></td><td>Beclometasone
(alone only when Aminosalicylates not tolerated)</td></tr>
<tr><td>Aminosalicylates</td><td>Mesalazine</td></tr>
<tr><td></td><td>Olsalazine</td></tr>
<tr><td></td><td>Balsalazide</td></tr>
<tr><td></td><td>Sulphasalazine</td></tr>
<tr><td>Immunomodulators</td><td>Methotrexate</td></tr>
<tr><td></td><td>Tacrolimus</td></tr>
<tr><td></td><td>Mycophenolate</td></tr>
<tr><td>Placebo</td><td></td></tr>
</table>

Excluded
• Azathioprine and Mercaptopurine – excluded as both considered for maintenance of remission.
• Hydrocortisone, Beclometasone and Budesonide excluded for children but included for adults.

The doses included are those considered effective for inducing remission for an acute exacerbation of ulcerative colitis.

Only drug treatments and preparations available in the UK are included.
</td>
</tr>
<tr>
<td>VI</td>
<td>Comparator</td>
<td>• Placebo
• Interclass comparisons
• Combinations of drugs
• Dose</td>
</tr>
</table>

VII	Outcomes	RRs will be used for outcomes
		• Clinical remission (author defined) at
		  ○ < 2weeks
		  ○ 2 to < 4 weeks
		  ○ 4 to < 6 weeks
		  ○ 6 to < 8weeks
		  ○ >8 weeks to 12 weeks
		• Withdrawal due to adverse events
		Quality of life (including short QOL questionnaire, IMPACT 3)

VIII	Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
IX	Other exclusion criteria	• Non English- language papers will be excluded • A trial duration limit of 12 weeks. Any drug taking longer than 12 weeks to have an effect would not be suitable for the induction of remission and more likely to be a maintenance treatment, unless 12 week data can be disaggregated. Protocols, abstracts, conference proceedings, theses, non-peer reviewed publications

X	Proposed sensitivity/sub-group analysis, or meta-regression	Data will be stratified based on:
		○ Dose – please see standard and high dose definitions in methods section.
		○ Mode of delivery:
		  ○ Topical (including foam enema, liquid enema and suppository) – suitable alone for proctitis
		  ○ Oral (including: modified release granule sachet modified release tablet, gastro-resistant tablets)
		  ○ Subcutaneous – methotrexate only
		
		Subgroups:
		○ Extent of disease
		  ○ proctitis
		  ○ proctosigmoiditis
		  ○ left-sided or extensive
		○ Mild/moderate disease
		○ Children, young people, adults

		If there is heterogeneity the following will be analysed separately: ○ Formulation (sachet, tablets, coated and not coated) ○ Regimen (for example, once versus twice a day)
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer
XII	Data management (software)	See Appendix B
XIII	Information sources – databases and dates	See appendix C of the relevant chapter
XIV	Identify if an update	Update of 2013 guideline
XV	Author contacts	Guideline updates team
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables). 10% of the data extraction were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B

XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
XXIV	Assessment of confidence in cumulative evidence	See Appendix B
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Tessa Lewis in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE 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.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

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Appendix B: Methods and process

Evidence synthesis and meta-analysis

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis.

Evidence of effectiveness of interventions

Quality assessment

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines' (2014). Randomised controlled trials (RCTs) are initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. The risk of bias of included RCTs was assessed using the Cochrane risk of bias tool (Higgins et al 2011). This tool assesses 6 domains: selection bias; performance bias; detection bias; attrition bias; reporting bias and any other bias. If more than 2 of: selection bias, performance bias, detection bias or attrition bias in a study were classed as unclear, the study was classed as having moderate risk of bias. Studies with no blinding (i.e. open-label trials) were considered at high risk of bias for subjective outcomes (quality of life and clinical remission). For the objective outcome, withdrawal due to adverse events, these studies were considered at moderate risk of bias, as the committee believed that assessing reasons for withdrawal may be subjected to less risk of bias. Studies which were single-blinded were considered at moderate risk of bias, as these may be subjected to less risk than open-labell trials.

No indirect study populations were included. Indirectness in terms of study treatment, if a study drug uses a formulation or route of administration which was not included in the protocol, was described in the evidence tables and in GRADE.

Methods for combining intervention evidence – pairwise meta-analysis

Meta-analysis of interventional data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Dichotomous outcomes were pooled on the odds ratio scale (using the Mantel–Haenszel method), which was a requirement for health economic modeling. Hazard ratios were also generated from the network meta-analysis of one outcome, withdrawal due to adverse events.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence, once pre-specified subgroup analyses had been undertaken to explore heterogeneity. Fixed-effect models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effect model were clearly not met (defined as $I^2 \geq 50\%$, which may reflect significant to considerable heterogeneity, as defined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011), random-effects results are presented.

As specified in the protocol, outcomes were stratified by mode of delivery and dose. Where it was possible to ascertain extent of disease in the study population, the outcomes were grouped by extent of disease. This was of particular interest for clinical remission, where data was further stratified by the following clinically important follow-up times:

- 0 to 2 weeks
- 3 to 4 weeks
- 5 to 8 weeks
- and 9 to 12 weeks.

The committee specified interest in finding which interventions had the highest overall withdrawal due to adverse events. Therefore, this outcome was not stratified by extent of disease. Paediatric studies were assessed separately. The majority of studies included reported severity as mild-to-moderate and there was limited evidence to allow stratification of data by severity.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

For odds ratios and hazard ratios where no other MID was available, the MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For continuous outcomes, a default MID interval of -0.5 and 0.5 were used.

GRADE for pairwise meta-analyses of interventional evidence

Grading of Recommendations Assessment Development and Evaluation (GRADE) was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 9.

Table 9: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.

GRADE criteria	Reasons for downgrading quality
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following two criteria were met:

- At least three treatment alternatives.
- A connected network to enable valid estimates to be made.

The outcome, clinical remission, was stratified by extent of disease. Separate NMAs were conducted for each important follow-up time. To avoid duplication of study samples and to maximise data available, the final follow-up times assessed were:

- 0 to 2 weeks,
- 0 to 4 weeks and
- 5 to 8 weeks.

Assessing inconsistency of network

Inconsistency (heterogeneity) concerns the differences in treatment effects between trials within each treatment contrast (Dias 2011b & 2013).

Inconsistency was assessed by comparing the chosen model (fixed or random effects) to an "inconsistency", or unrelated mean effects, model (Dias 2011b & 2013). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that inconsistency can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 distinct trials (van Valkenhoef 2016).

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 10: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses, the network was downgraded one level if the DIC for a random-effects model was lower than the DIC for a fixed-effect model.
Imprecision	The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or statistical significance if MIDs were not available.

Appendix C: Literature search strategies

C.1 Search history

Databases	Date searched	Version/files	No. retrieved	EndNote data (post de-dupe)
Cochrane Central Register of Controlled Trials (CENTRAL)	02/11/2017	Issue 10 of 12, October 2017	1025	758
Cochrane Database of Systematic Reviews (CDSR)	02/11/2017	Issue 11 of 12, November 2017	65	30
Database of Abstracts of Reviews of Effect (DARE)	02/11/2017	Issue 2 of 4, April 2015	62	11
Health Technology Assessment (HTA Database)	02/11/2017	Issue 4 of 4, October 2016	30	15
Embase (Ovid)	02/11/2017	1974 to 2017 Week 44	8906	6032
MEDLINE (Ovid)	02/11/2017	1946 to October Week 4 2017	3230	2544
MEDLINE In-Process (Ovid)	02/11/2017	November 01, 2017	303	269

In addition, additional search was undertaken on 05/12/2017 with the following lines:

Mycophenolic Acid/ (MeSH) mycophenolic acid/ (Emtree)

(Mycophen* or mofetil* or myfortic* or "rs 61443" or rs-61443 or rs61443 or "erl 080*" or erl080* or melbex* or "nsc 129185" or nsc129185).tw

Numbers for targeted Mycophenolate search:

Databases	Date searched	Version/files	No. retrieved	EndNote data (post de-dupe)
Cochrane Central Register of Controlled Trials (CENTRAL)	05/12/2017	Issue 11 of 12, November 2017	9	9
Cochrane Database of Systematic Reviews (CDSR)	05/12/2017	Issue 12 of 12, December 2017	0	0
Database of Abstracts of Reviews of Effect (DARE)	05/12/2017	Issue 2 of 4, April 2015	0	0
Health Technology Assessment (HTA Database)	05/12/2017	Issue 4 of 4, October 2016	0	0
Embase (Ovid)	05/12/2017	1974 to 2017 Week 49	48	35
MEDLINE (Ovid)	05/12/2017	1946 to Present with Daily Update	30	14

Databases	Date searched	Version/files	No. retrieved	EndNote data (post de-dupe)
MEDLINE In-Process (Ovid)	05/12/2017	December 04, 2017	3	0

1

2 A top-up search was undertaken on 06/08/2018:

Databases	Date searched	Version/files	No. retrieved	Post de-dupe
Cochrane Central Register of Controlled Trials (CENTRAL)	06/08/2018	Issue 7 of 12, July 2018	187	152
Cochrane Database of Systematic Reviews (CDSR)	06/08/2018	Issue 8 of 12, August 2018	2	1
Database of Abstracts of Reviews of Effect (DARE)	n/a	LEGACY DATABASE - NO UPDATE SINCE ORIGINAL SEARCH	0	0
Embase (Ovid)	06/08/2018	1974 to 2018 August 03	858	705
MEDLINE (Ovid)	06/08/2018	1946 to August 03, 2018	352	348
MEDLINE In-Process (Ovid)	06/08/2018	August 03, 2018	88	84
MEDLINE Epub Ahead of Print	06/08/2018	August 03, 2018	76	68
MHRA – Drug Safety Alerts	06/08/2018	n/a	0	n/a

3

C.2 Search strategy: medline

5 Combined search strategy for ulcerative colitis and Crohn's guideline updates:

Database: Medline
1 Colitis, Ulcerative/ (32987)
2 exp Proctitis/ (3053)
3 exp inflammatory bowel diseases/ (75028)
4 (inflamm* adj4 (colon* or bowel)).ti,ab. (39606)
5 (ulcer* adj4 colitis).tw. (32358)
6 (pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis).tw. (4083)
7 ((total or sub-total or subtotal or extensive or left-sided or universal) adj colitis).tw. (598)
8 or/1-7 (94390)
9 exp glucocorticoids/ (190101)
10 prednisolone/ (32971)
11 budesonide/ (4217)
12 beclomethasone/ (3030)
13 cortisone/ (20315)
14 hydrocortisone/ (71981)

Database: Medline

15 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (195985)

16 methotrexate/ (38313)

17 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (39039)

18 6-mercaptopurine/ (6315)

19 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (5586)

20 azathioprine/ (14798)

21 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (14464)

22 tacrolimus/ (15065)

23 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide).tw. (19144)

24 cyclosporine/ (29288)

25 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin).tw. (48758)

26 mesalamine/ (3355)

27 sulfasalazine/ (4249)

28 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or

Database: Medline

"meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (5768)

29 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (4733)

30 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (289)

31 or/9-30 (435912)

32 8 and 31 (12442)

33 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (4930039)

34 32 and 33 (3059)

35 exp crohn disease/ (37290)

36 ((crohn or crohn's or crohns) adj4 (disease* or colitis)).tw. (37837)

37 ((ileitis or enteritis) adj4 (terminal or regional)).tw. (1587)

38 ((colitis or enteritis) adj4 granuloma*).tw. (648)

39 ileocoli*.tw. (1925)

40 (epithelioid adj4 granuloma*).tw. (1842)

41 exp inflammatory bowel diseases/ (75028)

42 (inflamm* adj4 bowel).tw. (35973)

43 or/35-42 (92978)

44 exp glucocorticoids/ (190101)

45 dexamethasone isonicotinate/ or dexamethasone/ (51008)

46 fluprednisolone/ (281)

47 methylprednisolone hemisuccinate/ or methylprednisolone/ (19252)

48 prednisolone/ (32971)

49 prednisone/ (39961)

50 hydrocortisone/ (71981)

51 cortisone/ (20315)

52 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or diadresonf or predate or predonine or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (197102)

53 methotrexate/ (38313)

54 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or

Database: Medline

ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (39039)

55 6-mercaptopurine/ (6315)

56 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (5586)

57 azathioprine/ (14798)

58 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (14464)

59 mesalamine/ (3355)

60 sulfasalazine/ (4249)

61 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (5768)

62 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (4733)

63 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (289)

64 enteral nutrition/ (19487)

65 ((enteral* or force* or tube*) adj4 (nutrition* or feeding*)).tw. (18406)

66 food, formulated/ (6245)

67 exp food/ (1215042)

68 exp diet/ (258677)

69 lactose/ (11264)

70 ((polymeric or elemental or liquid or peptide or whole protein) adj (diet* or food* or formula*)).tw. (7013)

71 (formula* adj4 (diet* or food*)).tw. (5857)

72 ((diet or nutrition) adj therapy).tw. (3175)

73 enteral nutrition.tw. (6821)

74 dh.fs. (48474)

75 exp anti-bacterial agents/ (677899)

76 exp nitroimidazoles/ (18134)

Database: Medline

77 or/44-76 (2412648)
78 43 and 77 (19101)
79 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (4930039)
80 78 and 79 (4984)
81 Infliximab/ (9326)
82 (infliximab or "mab ca2" or remicade or avakine or flixabi or revellex).tw. (9412)
83 Adalimumab/ (4382)
84 (Adalimumab or d2e7 or humira).tw. (4481)
85 or/81-84 (14247)
86 43 and 85 (5079)
87 34 or 80 or 86 (9567)
88 Randomized Controlled Trial.pt. (497588)
89 Controlled Clinical Trial.pt. (99265)
90 Clinical Trial.pt. (547948)
91 exp Clinical Trials as Topic/ (332607)
92 Placebos/ (36441)
93 Random Allocation/ (99781)
94 Double-Blind Method/ (157733)
95 Single-Blind Method/ (26629)
96 Cross-Over Studies/ (45112)
97 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (990056)
98 (random$ adj3 allocat$).tw. (27830)
99 placebo$.tw. (192664)
100 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (154732)
101 (crossover$ or (cross adj over$)).tw. (71695)
102 or/88-101 (1755240)
103 Meta-Analysis.pt. (92040)
104 Network Meta-Analysis/ (226)
105 Meta-Analysis as Topic/ (17172)
106 Review.pt. (2334380)
107 exp Review Literature as Topic/ (10190)
108 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (107952)
109 (review$ or overview$).ti. (364972)
110 (systematic$ adj5 (review$ or overview$)).tw. (103479)
111 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (6797)
112 ((studies or trial$) adj2 (review$ or overview$)).tw. (34673)
113 (integrat$ adj3 (research or review$ or literature)).tw. (8116)
114 (pool$ adj2 (analy$ or data)).tw. (22232)
115 (handsearch$ or (hand adj3 search$)).tw. (7405)
116 (manual$ adj3 search$).tw. (4478)
117 or/103-116 (2543434)
118 102 or 117 (3977465)
119 87 and 118 (3791)
120 animals/ not humans/ (4648315)
121 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (1888307)
122 119 not (120 or 121) (3603)

Database: Medline	
123	limit 122 to english language (3230)

C.3 Health economics search strategy

C.3.1 Overview

Sources searched:

- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- Embase (Ovid)
- EconLit (Ovid)
- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)

Searches were carried out in November 2017 with a date limit of the previous guideline from March 2012 onwards. A top-up search was carried out in August 2018.

C.3.2 Search stratregy Ovid MEDLINE(R)

Database: Ovid MEDLINE(R)	
1	Colitis, Ulcerative/ (32987)
2	exp Proctitis/ (3053)
3	exp inflammatory bowel diseases/ (75028)
4	(inflamm* adj4 (colon* or bowel)).ti,ab. (39606)
5	(ulcer* adj4 colitis).tw. (32358)
6	(pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis).tw. (4083)
7	((total or sub-total or subtotal or extensive or left-sided or universal) adj colitis).tw. (598)
8	or/1-7 (94390)
9	exp glucocorticoids/ (190101)
10	prednisolone/ (32971)
11	budesonide/ (4217)
12	beclomethasone/ (3030)
13	cortisone/ (20315)
14	hydrocortisone/ (71981)
15	(beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog

Database: Ovid MEDLINE(R)

or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (195985)

16 methotrexate/ (38313)

17 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (39039)

18 6-mercaptopurine/ (6315)

19 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (5586)

20 azathioprine/ (14798)

21 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (14464)

22 tacrolimus/ (15065)

23 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide).tw. (19144)

24 cyclosporine/ (29288)

25 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin).tw. (48758)

26 mesalamine/ (3355)

27 sulfasalazine/ (4249)

28 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (5768)

29 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (4733)

Database: Ovid MEDLINE(R)

30 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (289)
31 or/9-30 (435912)
32 8 and 31 (12442)
33 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (4930039)
34 32 and 33 (3059)
35 Economics/ (27434)
36 exp "Costs and Cost Analysis"/ (222141)
37 Economics, Dental/ (1902)
38 exp Economics, Hospital/ (23287)
39 exp Economics, Medical/ (14356)
40 Economics, Nursing/ (3992)
41 Economics, Pharmaceutical/ (2967)
42 Budgets/ (11098)
43 exp Models, Economic/ (13757)
44 Markov Chains/ (13195)
45 Monte Carlo Method/ (27425)
46 Decision Trees/ (10674)
47 econom$.tw. (208611)
48 cba.tw. (9739)
49 cea.tw. (19814)
50 cua.tw. (951)
51 markov$.tw. (16071)
52 (monte adj carlo).tw. (28826)
53 (decision adj3 (tree$ or analys$)).tw. (11483)
54 (cost or costs or costing$ or costly or costed).tw. (407706)
55 (price$ or pricing$).tw. (29605)
56 budget$.tw. (21669)
57 expenditure$.tw. (45011)
58 (value adj3 (money or monetary)).tw. (1803)
59 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3472)
60 or/35-59 (837448)
61 "Quality of Life"/ (167314)
62 quality of life.tw. (197524)
63 "Value of Life"/ (5803)
64 Quality-Adjusted Life Years/ (10621)
65 quality adjusted life.tw. (9189)
66 (qaly$ or qald$ or qale$ or qtime$).tw. (7543)
67 disability adjusted life.tw. (2172)
68 daly$.tw. (2012)
69 Health Status Indicators/ (23476)
70 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (20634)
71 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1237)
72 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4144)

Database: Ovid MEDLINE(R)
73 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (23)
74 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (386)
75 (euroqol or euro qol or eq5d or eq 5d).tw. (6843)
76 (qol or hql or hqol or hrqol).tw. (36769)
77 (hye or hyes).tw. (65)
78 health$ year$ equivalent$.tw. (45)
79 utilit$.tw. (151862)
80 (hui or hui1 or hui2 or hui3).tw. (1134)
81 disutili$.tw. (331)
82 rosser.tw. (86)
83 quality of wellbeing.tw. (10)
84 quality of well-being.tw. (379)
85 qwb.tw. (198)
86 willingness to pay.tw. (3552)
87 standard gamble$.tw. (798)
88 time trade off.tw. (962)
89 time tradeoff.tw. (258)
90 tto.tw. (819)
91 or/61-90 (434819)
92 60 or 91 (1211787)
93 34 and 92 (211)
94 animals/ not humans/ (4648315)
95 93 not 94 (208)
96 limit 95 to english language (191)

C.3.13 Search strategy Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
1 Colitis, Ulcerative/ (0)
2 exp Proctitis/ (0)
3 exp inflammatory bowel diseases/ (11)
4 (inflamm* adj4 (colon* or bowel)).ti,ab. (4975)
5 (ulcer* adj4 colitis).tw. (2787)
6 (pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis).tw. (258)
7 ((total or sub-total or subtotal or extensive or left-sided or universal) adj colitis).tw. (40)
8 or/1-7 (6542)
9 exp glucocorticoids/ (1)
10 prednisolone/ (0)
11 budesonide/ (0)
12 beclomethasone/ (0)
13 cortisone/ (0)
14 hydrocortisone/ (0)
15 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (11841)

16 methotrexate/ (1)

17 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (2627)

18 6-mercaptopurine/ (0)

19 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (318)

20 azathioprine/ (0)

21 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (901)

22 tacrolimus/ (0)

23 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide).tw. (1315)

24 cyclosporine/ (0)

25 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin).tw. (1831)

26 mesalamine/ (0)

27 sulfasalazine/ (0)

28 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (497)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
29 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (279)
30 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (13)
31 or/9-30 (17564)
32 8 and 31 (695)
33 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (1815973)
34 32 and 33 (545)
35 Economics/ (2)
36 exp "Costs and Cost Analysis"/ (15)
37 Economics, Dental/ (1)
38 exp Economics, Hospital/ (0)
39 exp Economics, Medical/ (0)
40 Economics, Nursing/ (0)
41 Economics, Pharmaceutical/ (6)
42 Budgets/ (1)
43 exp Models, Economic/ (0)
44 Markov Chains/ (1)
45 Monte Carlo Method/ (0)
46 Decision Trees/ (0)
47 econom$.tw. (30506)
48 cba.tw. (312)
49 cea.tw. (1428)
50 cua.tw. (136)
51 markov$.tw. (3970)
52 (monte adj carlo).tw. (12728)
53 (decision adj3 (tree$ or analys$)).tw. (1403)
54 (cost or costs or costing$ or costly or costed).tw. (66586)
55 (price$ or pricing$).tw. (4210)
56 budget$.tw. (3661)
57 expenditure$.tw. (4687)
58 (value adj3 (money or monetary)).tw. (265)
59 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (463)
60 or/35-59 (115867)
61 "Quality of Life"/ (11)
62 quality of life.tw. (28398)
63 "Value of Life"/ (0)
64 Quality-Adjusted Life Years/ (0)
65 quality adjusted life.tw. (1160)
66 (qaly$ or qald$ or qale$ or qtime$).tw. (982)
67 disability adjusted life.tw. (343)
68 daly$.tw. (308)
69 Health Status Indicators/ (1)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
70 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2198)
71 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (561)
72 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (572)
73 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (6)
74 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (14)
75 (euroqol or euro qol or eq5d or eq 5d).tw. (1214)
76 (qol or hql or hqol or hrqol).tw. (5476)
77 (hye or hyes).tw. (5)
78 health$ year$ equivalent$.tw. (2)
79 utilit$.tw. (21827)
80 (hui or hui1 or hui2 or hui3).tw. (132)
81 disutili$.tw. (47)
82 rosser.tw. (5)
83 quality of wellbeing.tw. (3)
84 quality of well-being.tw. (22)
85 qwb.tw. (8)
86 willingness to pay.tw. (558)
87 standard gamble$.tw. (59)
88 time trade off.tw. (83)
89 time tradeoff.tw. (15)
90 tto.tw. (85)
91 or/61-90 (52080)
92 60 or 91 (161067)
93 34 and 92 (43)
94 animals/ not humans/ (225)
95 93 not 94 (43)
96 limit 95 to english language (42)

1

C.324 Search strategy Embase

3

Database: Embase
1 ulcerative colitis/
2 exp proctitis/
3 exp inflammatory bowel disease/
4 (inflamm* adj4 (colon* or bowel)).tw.
5 (ulcer* adj4 colitis).tw.
6 (pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis).tw.
7 ((total or sub-total or subtotal or extensive or left-sided or universal) adj colitis).tw.
8 or/1-7
9 exp glucocorticoid/

Database: Embase

10 prednisolone/

11 budesonide/

12 beclometasone/

13 cortisone/

14 hydrocortisone/

15 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw.

16 methotrexate/

17 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw.

18 mercaptopurine/

19 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw.

20 azathioprine/

21 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw.

22 tacrolimus/

23 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide).tw.

24 cyclosporin/

25 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin).tw.

26 mesalazine/

27 salazosulfapyridine/

Database: Embase

28 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw.

29 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw.

30 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw.

31 or/9-30

32 8 and 31

33 (201203* or 201204* or 201205* or 201206* or 201207* or 201208*or 201209* or 20121* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.

34 32 and 33

35 exp Health Economics/

36 exp "Health Care Cost"/

37 exp Pharmacoeconomics/

38 Monte Carlo Method/

39 Decision Tree/

40 econom$.tw.

41 cba.tw.

42 cea.tw.

43 cua.tw.

44 markov$.tw.

45 (monte adj carlo).tw.

46 (decision adj3 (tree$ or analys$)).tw.

47 (cost or costs or costing$ or costly or costed).tw.

48 (price$ or pricing$).tw.

49 budget$.tw.

50 expenditure$.tw.

51 (value adj3 (money or monetary)).tw.

52 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.

53 or/35-52

54 "Quality of Life"/

55 Quality Adjusted Life Year/

56 Quality of Life Index/

57 Short Form 36/

58 Health Status/

59 quality of life.tw.

60 quality adjusted life.tw.

61 (qaly$ or qald$ or qale$ or qtime$).tw.

Database: Embase
62 disability adjusted life.tw.
63 daly$.tw.
64 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
65 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
66 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
67 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
68 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
69 (euroqol or euro qol or eq5d or eq 5d).tw.
70 (qol or hql or hqol or hrqol).tw.
71 (hye or hyes).tw.
72 health$ year$ equivalent$.tw.
73 utilit$.tw.
74 (hui or hui1 or hui2 or hui3).tw.
75 disutili$.tw.
76 rosser.tw.
77 quality of wellbeing.tw.
78 quality of well-being.tw.
79 qwb.tw.
80 willingness to pay.tw.
81 standard gamble$.tw.
82 time trade off.tw.
83 time tradeoff.tw.
84 tto.tw.
85 or/54-84
86 53 or 85
87 34 and 86
88 nonhuman/ not human/
89 Abstract report/ or Conference abstract/ or Conference paper/ or Conference review/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt.
90 87 not (88 or 89)
91 limit 90 to english language

1

C.325 Search strategy EconLit

3

Database: EconLit
1 (inflamm* adj4 (colon* or bowel)).tw. (9)
2 (ulcer* adj4 colitis).tw. (4)
3 (pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis).tw. (0)
4 ((total or sub-total or subtotal or extensive or left-sided or universal) adj colitis).tw. (0)

Database: EconLit

5 or/1-4 (12)

6 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson).tw. (30)

7 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or "mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate).tw. (6)

8 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).tw. (1)

9 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim).tw. (1)

10 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide).tw. (4)

11 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin).tw. (9)

12 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476).tw. (1)

13 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or

Database: EconLit

benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin).tw. (0)

14 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal).tw. (0)

15 or/6-14 (49)

16 5 and 15 (1)

C.3.6 Search strategy NHS EED and HTA

Database: NHS EED and HTA

#1 [mh ^"Colitis, Ulcerative"]

#2 [mh Proctitis]

#3 [mh "inflammatory bowel diseases"]

#4 inflamm* near/4 (colon* or bowel):ti,ab,kw

#5 (ulcer* near/4 colitis):ti,ab,kw

#6 (pancolitis or rectitis or proctocolitis or procto-colitis or colorectitis or rectocolitis or recto-colitis or recto-sigmoiditis or rectosigmoiditis or procto-sigmoiditis or proctosigmoiditis or proctitis):ti,ab,kw

#7 (total or sub-total or subtotal or extensive or left-sided or universal) near/1 colitis:ti,ab,kw

#8 {or #1-#7}

#9 [mh glucocorticoids]

#10 [mh ^prednisolone]

#11 [mh ^budesonide]

#12 [mh ^beclomethasone]

#13 [mh ^cortisone]

#14 [mh ^hydrocortisone]

#15 (beclomethasone or betnelan or betnesol or betamethasone or aerobec forte or aerobec or aldecin or apo-beclomethasone or ascocortonyl or asmabec clickhaler or beclamet or beclazone or beclo azu or beclo asma or beclocort or becloforte or beclomet or beclometasone or budesonide or budenofalk or clobetasol or cortisone or deflazacort or depomedrone or depo-medrone or desoximetasone or dexamethasone or diflucortolone or efcortesol or entocort or flumethasone or hydrocortisone or kenalog or medrone or melengestrol or methylprednisolone or methylprednisone or prednisolone or prednisone or solucortel or solu-cortel or solumedrone or solu-medrone or triamcinolone or beclorhinol or becloturmant or beclovent or becodisk* or beconase or becotide or bemedrex or bronchocort or ecobec or filair or junik or nasobec or prolair or propaderm or qvar or respocort or sanasthmax or sanasthmyl or vancenase or vanceril or ventolair or viarin or fluocinonide or fluocortolone or fluorometholone or fluprednisolone or flurandrenolone or paramethasone or prednisolone or prednimustine or triamcinolone or kenalog or deflazacort or calcort or fludrocortisone or MMX or cortisol or cortifair or cortril or epicortisol or adreson):ti,ab,kw

#16 [mh ^methotrexate]

#17 ("4 amino 10 methylfolic acid" or "4 amino 10 methylpteroylglutamic acid" or "4 amino n10 methylpteroylglutamic acid" or methopterine or abitrexate or amethopterin* or ametopterine or antifolan or biotrexate or canceren or "cl 14377" or cl14377 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or "intradose MTX" or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrex* or methylaminopterin* or meticil or metoject or metotrex* or metrex or mexate* or

Database: NHS EED and HTA

"mpi 5004" or mpi5004 or MTX or neotrexate or nordimet or novatrex or "nsc 740" or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate* or texorate or trexall or xaken or zexate):ti,ab,kw

#18 [mh ^6-mercaptopurine]

#19 (?mercaptopurin* or leupurin* or "puri nethol" or puri-nethol or purimethol or purinethol or "6 thiohypoxanthine" or 6-thiohypoxanthine or "6 thiopurine" or 6-thiopurine or "bw 57 323h" or "bw 57-323h" or "bw 57323h" or "1,7-dihydro-6h-purine-6-thione" or "mercapto purine" or "6 mp" or classen or empurine or ismipur or leukerin or loulla or mercaleukin or mercaptopurin* or mercapurene or mern or mycaptine or "nsc 755" or nsc755 or "puri nethol" or puri-nethol or "purine 6 thiol" or "purine thiol" or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine):ti,ab,kw

#20 [mh ^azathioprine]

#21 (azathio* or azothiop* or immuran or Imuran* or imurel or arathiop* or aza-q or azafalk or azahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or "bw 57 322" or bw 57-322 or "bw 57322" or bw57-322 or bw57322 or colinsan or immurel or immuthera or imunen or imuprin or imurek or imuren or "nsc 39084" or nsc39084 or thioazeprine or thioprine or transimune or zytrim):ti,ab,kw

#22 [mh ^tacrolimus]

#23 ("fk 506" or fk-506 or fk506 or "fr 900506" or fr-900506 or fr900506 or prograf* or tacrolimus or advagraf or astagraf or envarsus or fujimycin or hecoria or modigraf or "mustopic oint" or protopic or protopy or tsukubaenolide):ti,ab,kw

#24 [mh ^cyclosporine]

#25 (ciclosporin* or cyclosporin* or sandimmun* or neoral or deximune or cipol-n or implanta or imusporin):ti,ab,kw

#26 [mh ^mesalamine]

#27 [mh ^sulfasalazine]

#28 (aminosalicyl* or 5-aminosalicyl* or 5-ASA or 5ASA or 5aminosalicyl* or pentasa or mesalazine or mesalamine or asacol or mezavant or ipocol or mesren or salofalk or asacolon or ascolitin or canasa or claversal or fivasa or lixacol or mesalamine or mesasal or "2 hydroxy 5 aminobenzoic acid" or "5 amino 2 hydroxybenzoic acid" or "5 aminosalicylate" or "5 aminosalicylic acid" or "5-asa 400" or apriso or asacolitin or asalex or asalit or asavixin or azalan or claversal or colitofalk or delzicol or fisalamine or fiv-asa or fivasa or kenzomyl or lialda or lixacol or mesacol or mesagran or mesalin or mesalmin or mesavance or mesavancol or mesavant or "mesren mr" or "meta aminosalicylic acid" or neoasa or norasa or pentacol or quintasa or rowasa or salisofar or salogran or sfrowasa or "spd 476" or spd476):ti,ab,kw

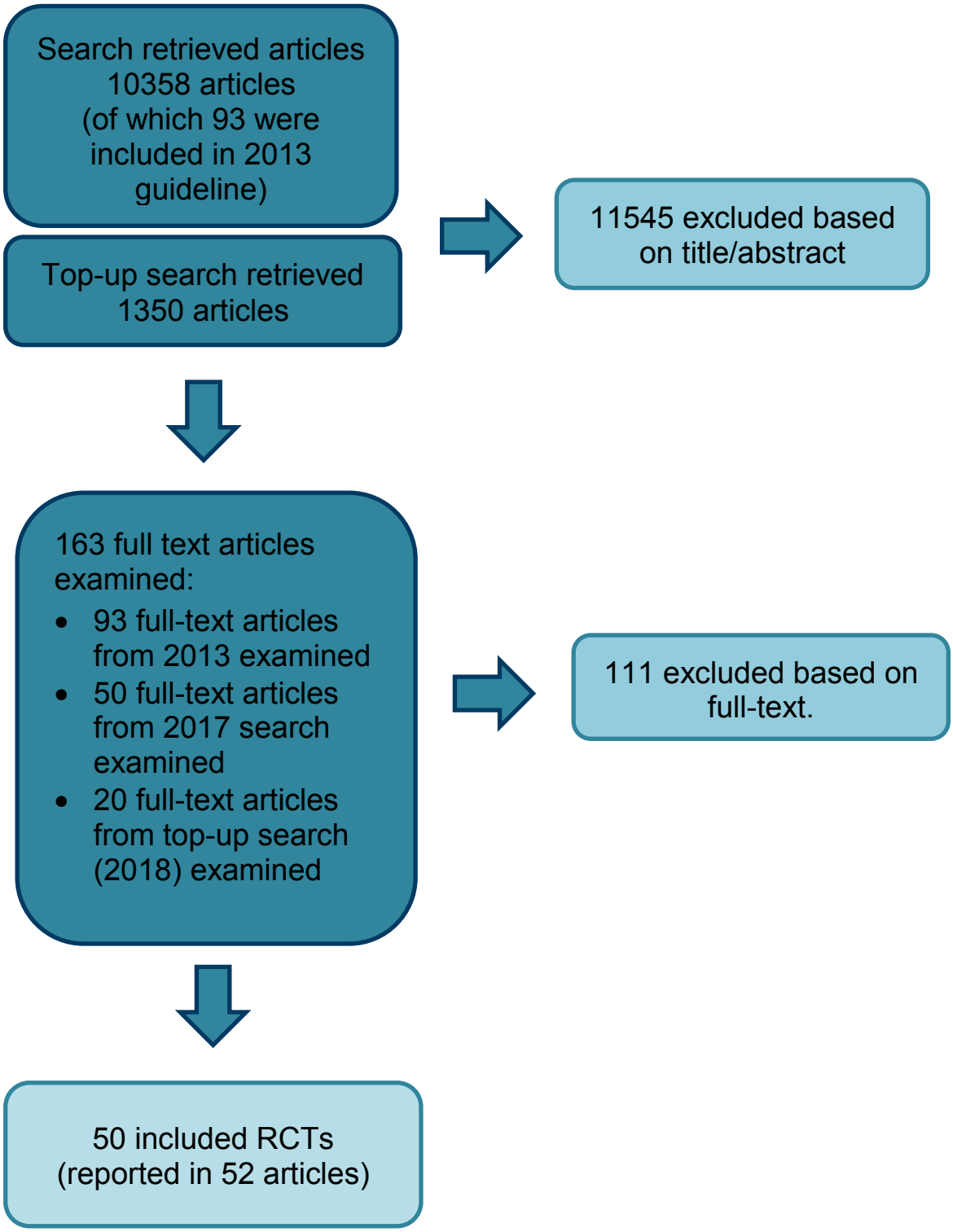
#29 (sulfasalazine* or sulphasalazine or salazopyrin* or salazosulfapyridine* or asulfidine* or "colo pleon" or colo-pleon or pleon or pyralin or azulfadine* or azulfidine* or salicylazosulfapyridine or ucine or ulcol or azopyrin* or azosulfidine or azulfid* or azulfin or benzosulfa or colopleon or disalazin or gastropyrin or "pleon ra" or "pyralin en" or rorasul or rosulfant or salazine or "salazo sulfapyridine" or salazodin or salazopirina or salazopyr* or salazopyrin* or salazosulf* or "salicyl azo sulfapyridine" or salicylazosulfapyridin* or salisulf or salopyr or saridine or "sas 500" or sulcolon or sulfasalizine or sulfosalazine or sulphosalazine or zopyrin):ti,ab,kw

#30 (olsalazine or balsalazide or dipentum or colazide or balsalazine or Giazo or Colazal):ti,ab,kw 128

#31 {or #9-#30}

#32 #8 and #31 Publication Year from 2012 to 2017

Appendix D: Clinical evidence study selection



Appendix E: References

E.1 Included clinical studies

E.1.1 Included studies from 2013 guideline

Bar-Meir S, Fidder H H, Faszczyk M, et al. (2003) Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. Diseases of the Colon and Rectum 46(7), 929-936

Binder V, Bondesen S, and Bonnevie O (1987) Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. Digestive Diseases and Sciences 32(6), 598-602

Campieri M, Defranchis R, Porro G B, et al. (1990) Mesalazine (5-Aminosalicyclic Acid) Suppositories in the Treatment of Ulcerative Proctitis Or Distal Proctosigmoiditis - A Randomized Controlled Trial. Scandinavian Journal of Gastroenterology 25(7), 663-668

Campieri M, Gionchetti P, Belluzzi A, et al. (1990) Topical Treatment with 5-Aminosalicylic in Distal Ulcerative-Colitis by Using A New Suppository Preparation - A Double-Blind Placebo Controlled Trial. International Journal of Colorectal Disease 5(2), 79-81

Campieri M, Gionchetti P, Belluzzi A, et al. (1991) Optimum Dosage of 5-Aminosalicylic Acid As Rectal Enemas in Patients with Active Ulcerative-Colitis. Gut 32(8), 929-931

Campieri M, Adamo S, Valpiani D, et al. (2003) Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Alimentary Pharmacology & Therapeutics 17(12), 1471-1480

Connolly M P, Poole C D, Currie C J, et al. (2009) Quality of life improvements attributed to combination therapy with oral and topical mesalazine in mild-to-moderately active ulcerative colitis. Digestion 80(4), 241-246

D'haens G, Hommes D, Engels L, et al. (2006) Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. Alimentary pharmacology & therapeutics 24(7), 1087–1097

Dick A P, Grayson M J, Carpenter R G, et al. (1964) Controlled Trial of Sulphasalazine In The Treatment Of Ulcerative Colitis. Gut 5, 437-442

Feurle G E, Theuer D, Velasco S, et al. (1989) Olsalazine Versus Placebo in the Treatment of Mild to Moderate Ulcerative-Colitis - A Randomized Double-Blind Trial. Gut 30(10), 1354-1361

Gionchetti P, Rizzello F, Venturi A, et al. (1998) Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. Diseases of the Colon & Rectum 41(1), 93-97

Gross V, Bar-Meir S, Lavy A, et al. (2006) Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. Alimentary Pharmacology and Therapeutics 23(2), 303-312

Gross V, Bunganic I, Belousova E A, et al. (2011) 3g mesalazine granules are superior to 9mg budesonide for achieving remission in active ulcerative colitis: a double-blind, double-dummy, randomised trial. Journal of Crohn's and colitis 5(2), 129-138

Hanauer S, Schwartz J, Robinson M, et al. (1993) Mesalamine Capsules for Treatment of Active Ulcerative-Colitis - Results of A Controlled Trial. American Journal of Gastroenterology 88(8), 1188-1197

Hanauer S B (1998) Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: Results of a multicentered placebo-controlled trial. Inflammatory Bowel Diseases 4(2), 79-83

Hanauer S B, Sandborn W J, Kornbluth A, et al. (2005) Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. American Journal of Gastroenterology 100(11), 2478-2485

Hetzel D J, Shearman D J.C, Bochner F, et al. (1986) Azodisalicylate (Olsalazine) in the Treatment of Active Ulcerative-Colitis - A Placebo Controlled Clinical-Trial and Assessment of Drug Disposition. Journal of Gastroenterology and Hepatology 1(3), 257-266

Irvine E J, Yeh C H, Ramsey D, et al. (2008) The effect of mesalazine therapy on quality of life in patients with mildly and moderately active ulcerative colitis. Alimentary Pharmacology and Therapeutics 28(11-12), 1278-1286

Ito H, Iida M, Matsumoto T, et al. (2010) Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. Inflammatory Bowel Diseases 16(9), 1567-1574

Kamm M A, Sandborn W J, Gassull M, et al. (2007) Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology 132(1), 66-75

Kruis W, Bar-Meir S, Feher J, et al. (2003) The optimal dose of 5-aminosalicylic acid in active ulcerative colitis: a dose-finding study with newly developed mesalamine. Clinical Gastroenterology and Hepatology 1(1), 36-43

Lauritsen K, Laursen L S, Bukhave K, et al. (1986) Effects of topical 5-aminosalicylic acid and prednisolone on prostaglandin E2 and leukotriene B4 levels determined by equilibrium in vivo dialysis of rectum in relapsing ulcerative colitis. Gastroenterology 91(4), 837-844

Lennard Jones J.E, Longmore A J, Newell A C, et al. F A (1960) An Assessment of Prednisone, Salazopyrin, and Topical Hydrocortisone Hemisuccinate Used As Out-Patient Treatment for Ulcerative Colitis. Gut 1(3), 217-222

Levine D S, Riff D S, Pruitt R, et al. (2002) A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. American Journal of Gastroenterology 97(6), 1398-1407

Lichtenstein G R, Kamm M A, Boddu P, et al. (2007) Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clinical Gastroenterology and Hepatology 5(1), 95-102

Marteau P, Probert C S, Lindgren S, et al. (2005) Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut 54(7), 960-965

Pokrotnieks J, Marlicz K, Paradowski L, et al. (2000) Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: A double-blind, randomized, placebo-controlled study. Alimentary Pharmacology & Therapeutics 14(9), 1191-1198

Pruitt R, Hanson J, Safdi M, et al. (2002) Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. American Journal of Gastroenterology 97(12), 3078-3086

Rizzello F, Gionchetti P, D'Arienzo A, et al. (2002) Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. Alimentary Pharmacology and Therapeutics 16(6), 1109-1116

Sandborn W J, Regula J, Feagan B G, et al. (2009) Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. Gastroenterology 137(6), 1934-1943

Sandborn WJ, Travis S, Moro L, et al. (2012) Once-Daily Budesonide MMX [REGISTERED] Extended-Release Tablets Induce Remission in Patients With Mild to Moderate Ulcerative Colitis: Results From the CORE I Study.. Gastroenterology 143(5), 1218

Scherl E J, Pruitt R, Gordon G L, et al. (2009) Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. American Journal of Gastroenterology 104(6), 1452-1459

Sninsky C A, Cort D H, Shanahan F, et al. (1991) Oral Mesalamine (Asacol) for Mildly to Moderately Active Ulcerative-Colitis - A Multicenter Study. Annals of Internal Medicine 115(5), 350-355

Vecchi M, Meucci G, Gionchetti P, et al. (2001) Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. Alimentary Pharmacology and Therapeutics 15(2), 251-256

E.1.2 Included studies from 2019 guideline update

Travis S P, Danese S, Kupcinskas L, et al. (2013) Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: Results from the randomised CORE II study. Inflammatory Bowel Disease Monitor 13(4), 161-162

Carbonnel F, Colombel J F, Filippi J, et al. (2016) Methotrexate Is Not Superior to Placebo for Inducing Steroid-Free Remission, but Induces Steroid-Free Clinical Remission in a Larger Proportion of Patients With Ulcerative Colitis. Gastroenterology 150(2), 380-8.e4

Feagan Bg, Sandborn Wj, D'Haens G, et al. (2013) The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology 145(1), 149-157

Lawrance Ic, Baird A, Lightower D, et al. (2017) Efficacy of Rectal Tacrolimus for Induction Therapy in Patients With Resistant Ulcerative Proctitis. Clinical gastroenterology and hepatology 15(8), 1248-1255

Naganuma M, Aoyama N, Suzuki Y, et al. (2016) Twice-daily Budesonide 2-mg Foam Induces Complete Mucosal Healing in Patients with Distal Ulcerative Colitis. Journal of Crohn's & colitis 10(7), 828-36

Naganuma M, Aoyama N, Tada T, et al. (2017) Complete mucosal healing of distal lesions induced by twice-daily budesonide 2-mg foam promoted clinical remission of mild-to-moderate ulcerative colitis with distal active inflammation: double-blind, randomized study. Journal of Gastroenterology, 1-13

Ogata H, Aoyama N, Mizushima S, et al. (2017) Comparison of efficacy of multimatrix mesalazine 4.8 g/day once-daily with other high-dose mesalazine in active ulcerative colitis: a randomized, double-blind study. Intestinal Research 15(3), 368-379

Pontes C, Vives R, Torres F, et al. (2014) Safety and activity of dersalazine sodium in patients with mild-to-moderate active colitis: double-blind randomized proof of concept study. Inflammatory Bowel Diseases 20(11), 2004-12

Probert Cs, Dignass Au, Lindgren S, et al. P (2014) Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. Journal of crohn's & colitis 8(3), 200-207

Rubin D, Cohen R, Sandborn W, et al. (2017) Budesonide Multimatrix Is Efficacious for Mesalamine-refractory, Mild to Moderate Ulcerative Colitis: A Randomised, Placebo-controlled Trial. Journal of Crohn's & colitis 11(7), 785-791

Sandborn Wj, Bosworth B, Zakko S, et al. (2015) Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology 148(4), 740-750.e2

Suzuki Y, Iida M, Ito H, et al. (2016) Efficacy and safety of two pH-dependent-release mesalamine doses in moderately active ulcerative colitis: a multicenter, randomized, double-blind, parallel-group study. Intestinal Research 14(1), 50-9

Travis Sp, Danese S, Kupcinskas L, et al. (2014) Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gut 63(3), 433-441

Watanabe M, Nishino H, Sameshima Y, et al. (2013) Randomised clinical trial: Evaluation of the efficacy of mesalazine (mesalamine) suppositories in patients with ulcerative colitis and active rectal inflammation - A placebo-controlled study. Alimentary Pharmacology and Therapeutics 38(3), 264-273

Winter H, Krzeski P, Heyman M, et al. (2014) High- and low-dose oral delayed-release mesalamine in children with mild-to-moderately active ulcerative colitis. Journal of pediatric gastroenterology and nutrition 59(6), 767-772

E.1.3 Included studies from top-up search

Ogata H, Yokoyama T, Mizushima S, et al. (2018) Comparison of efficacy of once daily multimatrix mesalazine 2.4 g/day and 4.8 g/day with other 5-aminosalicylic acid preparation in active ulcerative colitis: a randomized, double-blind study. Intestinal Research 16(2), 255-266

E.2 Included economic studies

E.2.1 Included studies from 2013 guideline

Brereton N, Bodger K, Kamm MA, Hodgkins P, Yan S, Akehurst R. (2010). A cost-effectiveness analysis of MMX mesalazine compared with mesalazine in the treatment of mild-to-moderate ulcerative colitis from a UK perspective. Journal of Medical Economics, 13(1), 148-161

Buckland A, Bodger K. (2008). The cost-utility of high dose oral mesalazine for moderately active ulcerative colitis. Alimentary Pharmacology & Therapeutics, 28(11), 1287-1296

Connolly MP, Nielsen SK, Currie CJ, Marteau P, Probert CS, Travis SP. (2009). An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-to-moderately active ulcerative colitis based on results from randomised controlled trial. Journal of Crohn's and Colitis, 3(3).168-174

Connolly MP, Kuyvenhoven JP, Postma MJ, Nielsen SK. (2014). Cost and quality-adjusted life year differences in the treatment of active ulcerative colitis using once-daily 4 g or twice-daily 2g mesalazine dosing. Journal of Crohn's and Colitis, 8(5), 357-362

E.3 Additional references

Bassi A, Dodd S, Williamson P, Bodger K. (2004). Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut, 53(10), 1471-1478

Dias, S, Welton, et al. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making. 2011; last updated April 2012; available from http://www.nicedsu.org.uk

Dias, S, Welton, et al. NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011; last updated September 2016; available from http://www.nicedsu.org.uk

Dias, S, Welton, NJ, et al. NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model. 2011; last updated April 2012; available from http://www.nicedsu.org.uk

Dias S, Welton NJ, et al. (2013). Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials. *Medical Decision Making*. 33(5):641–656.

Fenwick E, Claxton K, Sculpher M (2001). Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics. 10(8), 779-87

Kaltenthaler, E., Tappenden, P., Paisley, S., Squires, H. (2011). NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from http://www.nicedsu.org.uk

Modi A, Sen S, Adachi JD, et al. (2017). Association of gastrointestinal events with quality of life and treatment satisfaction in osteoporosis patients: results from the Medication Use Patterns, Treatment Satisfaction, and Inadequate Control of Osteoporosis Study (MUSIC OS). Osteoporosis International, 28(10), 2867-2876

Poole CD, Connolly MP, Nielsen SK, Currie CJ, Marteau P. (2010). A comparison of physician-rated disease severity and patient reported outcomes in mild to moderately active ulcerative colitis. Journal of Crohn's and Colitis, 4(3), 275-282

Royal College of Physicians. National clinical audit report of inpatient care for people with ulcerative colitis: adult national report. (2014). UK IBD audit. London: Royal College of Physicians.

Royal College of Physicians. National clinical audit of biological therapies: annual report. (2016). UK inflammatory bowel disease (IBD) audit. London: Royal College of Physicians.

E.4 Excluded clinical studies

E.4.1 Excluded studies which were included in 2013 guideline

Andus T, Kocjan A, Muser M, et al. (2008) A novel high-dose 1g mesalamine suppository (Salofalk) is as efficacious as a 500-mg TID suppositories in mild to moderate active ulcerative proctitis: A multicenter, randomized trial. Gastroenterology 134(4 Suppl 1), T1137

Andus T, Kocjan A, Muser M, et al. (2010) Clinical trial: a novel high-dose 1 g mesalamine suppository (Salofalk) once daily is as efficacious as a 500-mg suppository thrice daily in active ulcerative proctitis. Inflammatory Bowel Diseases 16(11), 1947-1956

Ardizzone S, Doldo P, Ranzi T, et al. (1999) Mesalazine foam (Salofalk (R) foam) in the treatment of active distal ulcerative colitis. A comparative trial vs Salofalk (R) enema. Italian Journal of Gastroenterology and Hepatology 31(8), 677-684

Baron J H, Connell A M, Kanaghinis T G, et al. (1962) Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. British Medical Journal 2(5302), 441-443

Baumgart D C, MacDonald J K, and Feagan B (2008) Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. Cochrane Database of Systematic Reviews (3),

Biancone L, Gionchetti P, Blanco G D.V, et al. (2007) Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: A multicenter, randomized, double-blind study. Digestive and Liver Disease 39(4), 329-337

Cai J T, Wu L F, Du Q, et al. (2001) Olsalazine versus sulfasalazine in the treatment of ulcerative colitis: Randomized controlled Clinical trial. Chinese Journal of Digestion 21(10), 593-595

Campieri M, Gionchetti P, Belluzzi A, et al. (1988) 5-Aminosalicylic Acid As Enemas Or Suppositories in Distal Ulcerative-Colitis. Journal of Clinical Gastroenterology 10(4), 406-409

Campieri M, Gionchetti P, Belluzzi A, et al. (1991) Sucralfate, 5-Aminosalicylic Acid and Placebo Enemas in the Treatment of Distal Ulcerative-Colitis. European Journal of Gastroenterology & Hepatology 3(1), 41-44

Campieri M, Paoluzi P, Dalbasio G, et al. (1993) Better Quality of Therapy with 5-Asa Colonic Foam in Active Ulcerative-Colitis - A Multicenter Comparative Trial with 5-Asa Enema. Digestive Diseases and Sciences 38(10), 1843-1850

Cortot A, Maetz D, Degoutte E, Delette O, et al. (2008) Mesalamine Foam Enema Versus Mesalamine Liquid Enema in Active Left-Sided Ulcerative Colitis. American Journal of Gastroenterology 103(12), 3106-3114

Danielsson A, Hellers G, Lyrenas E, et al. (1987) A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis. Scandinavian Journal of Gastroenterology 22(8), 987-992

Farup P G, Hovde O, Halvorsen F A, et al. (1995) Mesalazine Suppositories Versus Hydrocortisone Foam in Patients with Distal Ulcerative-Colitis - A Comparison of the Efficacy and Practicality of 2 Topical Treatment Regimens. Scandinavian Journal of Gastroenterology 30(2), 164-170

Farup P G, Hinterleitner T A, Lukas M, et al. (2001) Mesalazine 4 g daily given as prolonged-release granules twice daily and four times daily is at least as effective as prolonged-release tablets four times daily in patients with ulcerative colitis. Inflammatory Bowel Diseases 7(3), 237-242

Ferry G D, Kirschner B S, Grand R J, et al. (1993) Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial. Journal of Pediatric Gastroenterology and Nutrition 17(1), 32-38

Forbes A, Al-Damluji A, Ashworth S, et al. (2005) Multicentre randomized-controlled clinical trial of Ipocol, a new enteric-coated form of mesalazine, in comparison with Asacol in the treatment of ulcerative colitis. Alimentary Pharmacology and Therapeutics 21(9), 1099-1104

Friedman L S, Richter J M, Kirkham S E, et al. (1986) 5-Aminosalicylic Acid Enemas in Refractory Distal Ulcerative-Colitis - A Randomized, Controlled Trial. American Journal of Gastroenterology 81(6), 412-418

Gibson P R, Fixa B, Pekarkova B, et al. (2006) Comparison of the efficacy and safety of Eudragit-L-coated mesalazine tablets with ethylcellulose-coated mesalazine tablets in patients with mild to moderately active ulcerative colitis. Alimentary Pharmacology and Therapeutics 23(7), 1017-1026

Green J R.B, Lobo A J, Holdsworth C D, et al. (1998) Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. Gastroenterology 114(1), 15-22

Hanauer S B, Barish C, Pambianco D, et al. (1996) A multi-center, double-blind, placebo-controlled, dose-ranging trial of olsalazine for mild-moderately active ulcerative colitis. Gastroenterology 110, A921

Hanauer S B, Robinson M, Pruitt R, et al. (1998) Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: A dose-ranging study. Gastroenterology 115(3), 525-532

Hanauer S B, Sandborn W J, Dallaire C, et al. (2007) Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. Canadian Journal of Gastroenterology 21(12), 827-834

Hartmann F, Stein J, and BudMesa-Study Group (2010) Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. Alimentary Pharmacology and Therapeutics 32(3), 368-376

Hiwatashi N, Suzuki Y, Mitsuyama K, et al. (2011) Clinical trial: Effects of an oral preparation of mesalazine at 4 g/day on moderately active ulcerative colitis. A phase III parallel-dosing study. Journal of Gastroenterology 46(1), 46-56

Jewell D P, and Truelove S C (1974) Azathioprine in Ulcerative-Colitis - Final Report on Controlled Therapeutic Trial. British Medical Journal 4(5945), 627-630

Jiang X L, and Cui H F (2004) Different therapy for different types of ulcerative colitis in China. World Journal of Gastroenterology 10(10), 1513-1520

Kruis W, Kiudelis G, Racz I, et al. (2009) Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. Gut 58(2), 233-240

Lamet M, Ptak T, Dallaire C, et al. (2005) Efficacy and safety of mesalamine 1 g HS versus 500 mg BID suppositories in mild to moderate ulcerative proctitis: a multicenter randomized study. Inflammatory Bowel Diseases 11(7), 625-630

Lamet M (2011) A multicenter, randomized study to evaluate the efficacy and safety of mesalamine suppositories 1 g at bedtime and 500 mg Twice daily in patients with active mild-to-moderate ulcerative proctitis. Digestive Diseases and Sciences 56(2), 513-522

Lee F I, Jewell D P, Mani V, et al. (1996) A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. Gut 38(2), 229-233

Lemann M, Galian A, Rutgeerts P, et al. (1995) Comparison of Budesonide and 5-Aminosalicylic Acid Enemas in Active Distal Ulcerative-Colitis. Alimentary Pharmacology & Therapeutics 9(5), 557-562

Lindgren S, Lofberg R, Bergholm L, et al. (2002) Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis. Scandinavian Journal of Gastroenterology 37(6), 705-710

Lofberg R, Ostergaard Thomsen O, et al. (1994) Budesonide versus prednisolone retention enemas in active distal ulcerative colitis.[Erratum appears in Aliment Pharmacol Ther 1995 Apr;9(2):213]. Alimentary Pharmacology and Therapeutics 8(6), 623-629

Marakhouski Y, Fixa B, Holoman J, et al. (2005) A double-blind dose-escalating trial comparing novel mesalazine pellets with mesalazine tablets in active ulcerative colitis.[Erratum appears in Aliment Pharmacol Ther. 2005 Mar 15;21(6):793]. Alimentary Pharmacology and Therapeutics 21(2), 133-140

Meyers S, Sachar D B, Present D H, et al. (1987) Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulfasalazine. A prospective, randomized, placebo-controlled, double-blind, dose-ranging clinical trial. Gastroenterology 93(6), 1255-1262

Miglioli M, Brunetti G, Sturniolo G C, et al. (1989) Oral 5-ASA (Asacol) in mild ulcerative colitis. A randomized double blind dose ranging trial. Italian Journal of Gastroenterology 21(1 SUPPL.), 7-8

Mulder C J, Tytgat G N, Weterman I T, et al. (1988) Double-blind comparison of slow-release 5-aminosalicylate and sulfasalazine in remission maintenance in ulcerative colitis. Gastroenterology 95(6), 1449-1453

Ogata H, Matsui T, Nakamura M, et al. (2006) A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis.[Erratum appears in Gut. 2006 Nov;55(11):1684 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected; Dosage error in article text]. Gut 55(9), 1255-1262

Ogata H, Kato J, Hirai F, et al. (2012) Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroidrefractory ulcerative colitis.. Inflammatory Bowel Diseases. 18(5), 803-808

Oren R, Arber N, Odes S, et al. (1996) Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. Gastroenterology 110(5), 1416-1421

Porro G B, Prantera C, Campieri M, et al. (1994) Comparative trial of methylprednisolone and budesonide enemas in active distal ulcerative colitis. European Journal of Gastroenterology and Hepatology 6(2), 125-130

Powell-Tuck J, Bown R L, and Lennard-Jones J E (1978) A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scandinavian Journal of Gastroenterology 13(7), 833-837

Powell-Tuck J, Macrae K D, Healy M J.R, et al. (1986) A Defense of the Small Clinical-Trial - Evaluation of 3 Gastroenterological Studies. British Medical Journal 292(6520), 599-602

Prantera C, Viscido A, Biancone L, et al. (2005) A new oral delivery system for 5-ASA: Preliminary clinical findings for MMx. Inflammatory Bowel Diseases 11(5), 421-427

Raedler A, Behrens C, and Bias P (2004) Mesalazine (5-aminosalicylic acid) micropellets show similar efficacy and tolerability to mesalazine tablets in patients with ulcerative colitis--

results from a randomized-controlled trial. . Alimentary pharmacology & therapeutics 20(11-12), 1353-1363

Rijk M C.M, and Tongerson J H.M (1991) The efficacy and safety of sulphasalazine and olsalazine in patients with active ulcerative colitis. Gastroenterology 100, A243

Rizzello F, Gionchetti P, Galeazzi R, et al. (2001) Oral beclomethasone dipropionate in patients with mild to moderate ulcerative colitis: a dose-finding study. Advances in Therapy 18(6), 261-271

Robinson M, Gitnick G, Balart L, et al. (1988) Olsalazine in the treatment of mild to moderate ulcerative colitis. Gastroenterology 84, A381

Romano C, Famiani A, Comito D, et al. (2010) Oral beclomethasone dipropionate in pediatric active ulcerative colitis: a comparison trial with mesalazine. Journal of Pediatric Gastroenterology and Nutrition 50(4), 385-389

Schroeder K W, Tremaine W J, and Ilstrup D M (1987) Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative-Colitis - A Randomized Study. New England Journal of Medicine 317(26), 1625-1629

Selby W S, Barr G D, and Ireland A (1985) Olsalazine in active ulcerative colitis. British Medical Journal 291(6506), 1373-1375

Shivananda S, Lennard-Jones J, Logan R, et al. (1996) Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). . Gut 39(5), 690-697

Sood A, Midha V, Sood N, et al. (2002) Methylprednisolone acetate versus oral prednisolone in moderately active ulcerative colitis. Indian Journal of Gastroenterology 21(1), 11-13

Sood A, Kaushal V, Midha V, et al. (2002) The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. Journal of Gastroenterology 37(4), 270-274

Tarpila S, Turunen U, Seppala K, et al. (1994) Budesonide enema in active haemorrhagic proctitis--a controlled trial against hydrocortisone foam enema. Alimentary Pharmacology and Therapeutics 8(6), 591-595

van Bodegraven A A, Boer R O, Lourens J, et al. W (1996) Distribution of mesalazine enemas in active and quiescent ulcerative colitis. Alimentary Pharmacology and Therapeutics 10(3), 327-332

Williams C N, Haber G, and Aquino J A (1987) Double-Blind, Placebo-Controlled Evaluation of 5-Asa Suppositories in Active Distal Proctitis and Measurement of Extent of Spread Using Tc-99M-Labeled 5-Asa Suppositories. Digestive Diseases and Sciences 32(12), S71-S75

Willoughby C P, Campieri M, and Lanfranchi G (1986) 5-Aminosalicylic acid (Pentasa) in enema form for the treatment of active ulcerative colitis. Italian Journal of Gastroenterology 18(1), 15-17

Zinberg J, Molinas S, and Das K M (1990) Double-Blind Placebo-Controlled Study of Olsalazine in the Treatment of Ulcerative-Colitis. American Journal of Gastroenterology 85(5), 562-566

E.4.2 Excluded studies from 2019 guideline update

Akobeng A K, Zhang D, Gordon M, et al. (2016) Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews 2016(9), CD003715

Assche G, Manguso F, Zibellini M, et al. (2015) Oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study. American journal of gastroenterology 110(5), 708-715

Assche G, Manguso F, Zibellini M, et al. (2015) Erratum: oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study (American Journal of Gastroenterology (2015) 110 (708-715) DOI: 10.1038/ajg.2015.114). American journal of gastroenterology 110(6), 943

Balzola F, Cullen G, Hoentjen F, et al. (2013) Randomised clinical trial: Once- Vs. twice-daily prolonged-release mesalazine for active ulcerative colitis. Inflammatory Bowel Disease Monitor 13(4), 160-161

Chande N, Wang Y, MacDonald J K, et al. (2014) Methotrexate for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews (8), CD006618

Chen M (2015) Pentasa enema may be superior to salofalk or glucocorticoid in patients with left-sided active ulcerative colitis. Journal of digestive diseases. 16, 96

Crispino P, Cassieri C, Zippi M, et al. (2015) Efficacy of mesalazine or beclomethasone dipropionate enema or their combination in patients with distal active ulcerative colitis. Italian journal of medicine. 9, 28

Cuffari C, Pierce D, Korczowski B, et al. (2016) Randomized clinical trial: pharmacokinetics and safety of multimatrix mesalamine for treatment of pediatric ulcerative colitis. Drug design, and development and therapy 10, 593-607

D'Haens Gr, Sandborn Wj, Zou G, et al. (2017) Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis. Alimentary pharmacology & therapeutics 46(3), 292-302

Dhaka N, Sharma A, Samanta J, et al. (2016) Randomized controlled trial comparing the efficacy of measalamine and oral steroids in patients with moderately active ulcerative colitis. Journal of gastroenterology and hepatology (australia). Conference: asia pacific digestive week, and APDW 2016. Japan. Conference start: 20161102. Conference end: 20161105 31, 165

Flourié B, Hagège H, Tucat G, et al. (2013) Randomised clinical trial: once- vs. twice-daily prolonged-release mesalazine for active ulcerative colitis. Alimentary pharmacology & therapeutics 37(8), 767-775

Ford A, Khan K, Achkar J, et al. (2012) Efficacy of oral vs topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis (Structured abstract). American Journal of Gastroenterology 107(2), 167-176

Hindryckx P, Zou G, Feagan B, et al. (2017) Biologic drugs for induction and maintenance of remission in Crohn's disease: a network meta-analysis. Cochrane Database of Systematic Reviews (8),

Kawakami K, Inoue T, Murano M, et al. (2015) Effects of oral tacrolimus as a rapid induction therapy in ulcerative colitis. World Journal of Gastroenterology 21(6), 1880-1886

Komaki Y, Komaki F, Ido A, et al. (2016) Efficacy and Safety of Tacrolimus Therapy for Active Ulcerative Colitis; A Systematic Review and Meta-analysis. Journal of Crohn's & colitis 10(4), 484-94

Kruis W, Brandes J W, Schreiber S, et al. (1998) Olsalazine versus mesalazine in the treatment of mild to moderate ulcerative colitis. Alimentary Pharmacology and Therapeutics 12(8), 707-715

Lasa J, and Olivera P (2017) Efficacy of Tacrolimus for Induction of Remission in Patients with Moderate-to-Severe Ulcerative Colitis: A Systematic Review and Meta-Analysis. Arquivos de Gastroenterologia 54(2), 167-172

Lie M R, Kanis S L, Hansen B E, et al. (2014) Drug therapies for ulcerative proctitis: systematic review and meta-analysis. Inflammatory Bowel Diseases 20(11), 2157-78

Manguso F, Bennato R, Lombardi G, et al. (2016) Efficacy and Safety of Oral Beclomethasone Dipropionate in Ulcerative Colitis: A Systematic Review and Meta-Analysis. PLoS ONE [Electronic Resource] 11(11), e0166455

Mate-Jimenez J, Hermida C, Cantero-Perona J, and Moreno-Otero R (2000) 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. European Journal of Gastroenterology and Hepatology 12(11), 1227-1233

Nguyen G C, Gulamhusein A, and Bernstein C N (2013) Erratum: 5-aminosalicylic acid is not protective against colorectal cancer in inflammatory bowel disease: A meta-analysis of non-

referral populations (American Journal of Gastroenterology (2012) 107 (1298-1304) DOI:10.1038/ajg.2012.198). American Journal of Gastroenterology 108(2), 292

Pica R, Unim H, Cassieri C, et al. (2013) Oral beclomethasone dipropionate vs 5-ASA enema in active UC: lower efficacy but better compliance. Journal of gastroenterology and hepatology. 28, 577

Pica R, Cassieri C, Cocco A, et al. (2015) A randomized trial comparing 4.8 vs. 2.4 g/day of oral mesalazine for maintenance of remission in ulcerative colitis. Digestive & Liver Disease 47(11), 933-7

Raskin J, Kamm M, Jamal M, et al. (2014) Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials. Gastroenterology 147(4), 793-802

Rubin D T, Bradette M, Gabalec L, et al. (2016) Ulcerative Colitis Remission Status After Induction With Mesalazine Predicts Maintenance Outcomes: the MOMENTUM Trial. Journal of Crohn's & colitis 10(8), 925-933

Sun J, and Yuan Y (2016) Mesalazine Modified-Release Tablet in the Treatment of Ulcerative Colitis in the Remission Phase: A Chinese, Multicenter, Single-Blind, Randomized Controlled Study. Advances in Therapy 33(3), 410-22

Turner D, Yerushalmi B, Kori M, et al. (2016) Once versus twice daily mesalazine to induce remission in pediatric ulcerative colitis: an investigator-initiated randomized controlled trial. Journal of pediatric gastroenterology and nutrition. 62, 86-87

Turner D, Yerushalmi B, Kori M, et al. (2017) Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial. Journal of Crohn's & colitis 11(5), 527-533

Van Assche, Gert , Manguso Francesco, Zibellini Marco, et al. (2015) Corrigendum: Oral Prolonged Release Beclomethasone Dipropionate and Prednisone in the Treatment of Active Ulcerative Colitis: Results From a Double-Blind, Randomized, Parallel Group Study.[Erratum for Am J Gastroenterol. 2015 May;110(5):708-15; PMID: 25869389]. American Journal of Gastroenterology 110(6), 943

Wang J, Shi Y, and Liu Z (2016) Efficacy of single vs multiple doses of 5-aminosalicylic acid (5-ASA) in the treatment of mild-moderate ulcerative colitis: An open randomized clinical trial. International Journal of Clinical and Experimental Medicine 9(11), 21654-21662

Wang Y, Parker C E, Bhanji T, et al. (2016) Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 4, CD000543

Zeng J, Lv L, and Mei Z C (2017) Budesonide foam for mild to moderate distal ulcerative colitis: A systematic review and meta-analysis. Journal of Gastroenterology & Hepatology 32(3), 558-566

Zhao X, Li N, Ren Y, et al. (2016) Efficacy and Safety of Beclomethasone Dipropionate versus 5-Aminosalicylic Acid in the Treatment of Ulcerative Colitis: A Systematic Review and Meta-Analysis. PLoS ONE [Electronic Resource] 11(8), e0160500

Zhao Xiaojing, Zhou Changcheng, Ma Jingjing, et al. (2017) Efficacy and safety of rectal 5-aminosalicylic acid versus corticosteroids in active distal ulcerative colitis: a systematic review and network meta-analysis. Scientific Reports 7, 46693

Zhu Y, Tang R K, Zhao P, et al. (2012) Can oral 5-aminosalicylic acid be administered once daily in the treatment of mild-to-moderate ulcerative colitis? A meta-analysis of randomized-controlled trials. European Journal of Gastroenterology & Hepatology 24(5), 487-94

E.4.3 Excluded studies from top-up search

Chande N, Wang Y, Macdonald J K, and McDonald J W. D (2014) Methotrexate for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2017(12), CD006618

D'Haens G R, Sandborn W J, Zou G, Stitt L W, Rutgeerts P J, Gilgen D, Jairath V, Hindryckx P, Shackelton L M, Vandervoort M K, Parker C E, Muller C, Pai R K, Levchenko O, Marakhouski Y, Horynski M, Mikhailova E, Kharchenko N, Pimanov S, and Feagan B G (2017) Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis. Alimentary Pharmacology & Therapeutics 46(3), 292-302

Dignass Axel, Schnabel Robert, Romatowski Jacek, Pavlenko Vladimir, Dorofeyev Andrey, Derova Jelena, Jonaitis Laimas, Dilger Karin, Nacak Tanju, Greinwald Roland, and International S A. T. Study Group (2018) Efficacy and safety of a novel high-dose mesalazine tablet in mild to moderate active ulcerative colitis: a double-blind, multicentre, randomised trial. United European Gastroenterology Journal 6(1), 138-147

Kato S, Kani K, Kurihara H, Ohmori T, and Yakabi K (2018) Comparison of rectal and oral mesalazine for treatment of rectal ulcerative proctitis: a prospective randomised clinical trial (CORRECT study). Journal of crohn's and colitis. Conference: 13th congress of European crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S434

Kokkinidis D G, Bosdelekidou E E, Iliopoulou S M, Tassos A G, Texakalidis P T, Economopoulos K P, and Kousoulis A A (2017) Emerging treatments for ulcerative colitis: a systematic review. Scandinavian Journal of Gastroenterology 52(9), 923-931

Komaki Y, Komaki F, Micic D, Yamada A, Suzuki Y, and Sakuraba A (2017) Pharmacologic therapies for severe steroid refractory hospitalized ulcerative colitis: A network meta-analysis. Journal of Gastroenterology & Hepatology 32(6), 1143-1151

Kreijne Je, Lie Mr, Dijkstra G, Lowenberg M, Assche G, West Rl, Noord D, Meulen-De Jong Aa, Hansen Be, Vries Ac, and Woude Cj (2018) Tacrolimus suppositories as induction therapy for refractory ulcerative proctitis: a randomised controlled trial. Journal of crohn's and

colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S45

Lasa J, Rausch A, and Zubiaurre I (2018) Efficacy and safety of anti-integrin antibodies in inflammatory bowel disease: Systematic review and meta-analysis. Acta Gastroenterologica Latinoamericana 48(2), 106-116

Lawrance I C, Baird A, Lightower D, Radford-Smith G, Andrews J M, and Connor S (2017) Efficacy of Rectal Tacrolimus for Induction Therapy in Patients With Resistant Ulcerative Proctitis. Clinical Gastroenterology & Hepatology 15(8), 1248-1255

Loftus Ev, Sands Be, Colombel J-F, Dotan I, Khalid Jm, Tudor D, and Geransar P (2018) Sustained corticosteroid-free remission with vedolizumab in moderate-to-severe ulcerative colitis: a post hoc analysis of GEMINI 1. Journal of crohn's and colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S317-s318

Fang WB, and Cai QF (2018) Mesalazine combined with golden bifid for treatment of patients with ulcerative colitis: effect on inflammatory response and anorectal motility. World chinese journal of digestology 26(10), 594-600

Perez-Calle J L, and Lopez-Serrano P (2016) Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulce-rative colitis. Enfermedad Inflamatoria Intestinal al Dia 15(2), 76-78

Roblin X, Paul S, Boschetti G, Phelip Jm, Tedesco E, Berger A, Nancey S, Williet N, and Flourie B (2018) Interest in the addition of azathioprine (AZA) to the switch of anti-TNF in IBD patients in loss of response with undetectable anti-TNF trough levels and anti-drug antibodies: a prospective randomised trial. Journal of crohn's and colitis. Conference: 13th congress of european crohn's and colitis organisation, and ECCO 2018. Austria 12(Supplement 1), S414-s415

Rubin D T, Cohen R D, Sandborn W J, Lichtenstein G R, Axler J, Riddell R H, Zhu C, Barrett A C, Bortey E, and Forbes W P (2017) Budesonide Multimatrix Is Efficacious for Mesalamine-refractory, Mild to Moderate Ulcerative Colitis: A Randomised, Placebo-controlled Trial. Journal of Crohn's & colitis 11(7), 785-791

Sherlock M E, Macdonald J K, Griffiths A M, Steinhart A H, and Seow C H (2015) Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2015(10), CD007698

Simadibrata Marcellus, Halimkesuma Christopher Christian, and Suwita Benedicta Mutiara (2017) Efficacy of Curcumin as Adjuvant Therapy to Induce or Maintain Remission in Ulcerative Colitis Patients: an Evidence-based Clinical Review. Acta Medica Indonesiana 49(4), 363-368

Turner Dan, Yerushalmi Baruch, Kori Michal, Broide Efrat, Mozer-Glassberg Yael, Shaoul Ron, Kolho Kaija-Leena, Shteyer Eyal, Shamaly Hussein, Ledder Oren, Cohen Shlomi, Peleg Sarit, On Avi, and Levine Arie (2016) Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial. Journal of Crohn's & colitis 03, 03

Turner D, Yerushalmi B, Kori M, Broide E, Mozer-Glassberg Y, Shaoul R, Kolho K L, Shteyer E, Shamaly H, Ledder O, Cohen S, Peleg S, On A, and Levine A (2017) Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial. Journal of Crohn's & colitis 11(5), 527-533

van Gennep , Sara , de Boer , Nanne K, D'Haens Geert R, and Lowenberg Mark (2017) Thiopurine Treatment in Ulcerative Colitis: A Critical Review of the Evidence for Current Clinical Practice. Inflammatory Bowel Diseases 24(1), 67-77

Appendix F:Clinical evidence tables

Study & population	Arms	Outcomes				Limitations
Bar-Meir et al. (2003)						
Extent: (1) proctitis n=38, proctosigmoiditis n=82 (2) proctitis n=43, proctosigmoiditis n=85 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: Mesalazine Definition of remission: DAI =< 3.	(1) N=120 Drug(s): budesonidebudesonide - topical (foam) Dose: 2mg (2) N=128 Drug(s): standard-dose hydrocortisone - topical (foam) Dose: 100mg		budesonide - topical (foam)	hydrocortisone - topical (foam)		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: HIGH – open-label Detection bias: Blinding of outcome assessment: HIGH – open-label Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: UNCLEAR Overall: HIGH
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	64/120	67/128	1.02 (CI: 0.81, 1.29)	
Binder et al. (1987)						
Extent: (1) numbers not given (2) numbers not given	(1) N=56 Drug(s): mesalazine - topical (liquid enema) Dose: 1g		mesalazine - topical (liquid enema)	prednisolone - topical (liquid enema)	RR	Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias:

Study & population	Arms	Outcomes				Limitations
Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 14 years and over Concomitant therapy: 'Maintenance treatment with/without SASP' Definition of remission: Change in disease activity acording to Binder et al.	(2) N=61 Drug(s): prednisolone - topical (liquid enema) Dose: 25mg		n/N	n/N		Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: HIGH Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: MODERATE
		Response: Clinical remission – 2wk	27/56	19/61	1.55 (CI: 0.98, 2.46)	
Campieri et al. (1990)						
Extent: (1) <20cm, distal sigmoid colon and rectum on sigmoidoscopy (2) <20cm, distal sigmoid colon and rectum on sigmoidoscopy Extent classification: Proctitis Severity: mild-to-moderate Age: 18 years and over	(1) N=32 Drug(s): mesalazine - topical (suppository) Dose: 1.5g (500mg asacol 3x day) (2) N=30 Drug(s): placebo		mesalazine - topical (suppository)	placebo		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: UNCLEAR Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias:
			n/N	n/N	RR	
		Response: Clinical remission – 2wk	8/32	1/30	7.50 (CI: 1.00, 56.44)	
		Clinical remission – 4wk	18/32	2/30	8.44 (CI: 2.14, 33.32)	

Study & population	Arms	Outcomes				Limitations
Concomitant therapy: SASP Definition of remission: Complete disappearance of symptoms.						LOW Overall: MODERATE
Campieri et al. (1990a)						
Extent: (1) proctitis n=23, distal proctosigmoiditis n=9 (2) proctitis n=19, distal proctosigmoiditis n=12 (3) proctitis n=23, distal proctosigmoiditis n=8 Extent classification: Proctitis Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: Mesalazine or SASP permitted Definition of remission: Symptomless, with no more than 2	(1) N=32 Drug(s): mesalazine - topical (suppository) Dose: 1g asacol (2x 500mg suppository) (2) N=31 Drug(s): mesalazine - topical (suppository) Dose: 1.5g (3x 500mg suppository) (3) N=31 Drug(s): placebo		mesalazine (asacol) - topical (suppository)	placebo		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: UNCLEAR Detection bias: Blinding of outcome assessment: UNCLEAR Attrition bias: Incomplete outcome data: HIGH (>10% difference in missing data in placebo arm.) Selective reporting: UNCLEAR Other bias: UNCLEAR Overall: MODERATE
			n/N	n/N	RR	
		Response: Clinical remission – 2wk	13/32	7/31	1.80 (CI: 0.83, 3.90)	
		Clinical remission – 4wk	22/32	12/31	1.78 (CI: 1.08, 2.93)	
			mesalazine - topical (suppository)	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 2wk	14/31	7/31	2.00 (CI: 0.94, 4.27)	
		Clinical remission – 4wk	23/31	12/31	1.92 (CI: 1.18, 3.13)	

<table>
<tr><th>Study & population</th><th>Arms</th><th>Outcomes</th><th>Limitations</th></tr>
<tr><td>bowel movements/ day without visible blood.</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Campieri et al. (1991)</td></tr>
<tr><td>Extent:
(1) proctitis n=7, proctosigmoiditis n=8, left sided colitis n=12
(2) proctitis n=8, proctosigmoiditis n=10, left sided colitis n=9
(3) proctitis n=10, proctosigmoiditis n=9, left sided colitis n=11
Extent classification: Proctosigmoiditis and left sided
Severity: mild
Age: 18 years and over
Concomitant therapy: SASP
Definition of remission: Symptoms of active disease resolved.</td><td>(1) N=27
Drug(s): mesalazine - topical (liquid enema)
Dose: 1g (unknown)
(2) N=27
Drug(s): placebo
(3) N=30
Drug(s): mesalazine - topical (liquid enema)
Dose: 2g (unknown)</td><td><table><tr><td></td><td>mesalazine - topical (liquid enema)</td><td>placebo</td><td></td></tr><tr><td></td><td>n/N</td><td>n/N</td><td>RR</td></tr><tr><td>Response:
Clinical remission – 2wk</td><td>9/27</td><td>1/27</td><td>9.00 (CI: 1.22, 66.23)</td></tr><tr><td>Clinical remission – 4wk</td><td>17/27</td><td>3/27</td><td>5.67 (CI: 1.88, 17.12)</td></tr></table></td><td>Selection bias
Random sequence generation: UNCLEAR
Allocation concealment: UNCLEAR
Performance bias:
Blinding of participants/personnel: LOW
Detection bias:
Blinding of outcome assessment: LOW
Attrition bias:
Incomplete outcome data: UNCLEAR
Selective reporting:
UNCLEAR
Other bias:
UNCLEAR
Overall: LOW</td></tr>
</table>

Study & population	Arms	Outcomes				Limitations
			mesalazine - topical (liquid enema)	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 2wk	11/30	1/27	9.90 (CI: 1.37, 71.70)	
		Clinical remission – 4wk	20/30	3/27	6.00 (CI: 2.00, 17.96)	
			mesalazine - topical (suppository)	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 2wk	9/27	1/27	9.00 (CI: 1.22, 66.23)	
		Clinical remission – 4wk	17/27	3/27	5.67 (CI: 1.88, 17.12)	
Carbonnel et al. (2016)						
Extent: Extensive Severity: moderate Age: < 75 years Concomitant therapy: Prednisolone. Ondansetron was allowed. Definition of remission: Mayo score ≤ 2 with no item > 1 and	(1) N = 60 Drug: methotrexate (subcutaneous or IV) Dose: 25 mg weekly (2) N = 51 Drug: Placebo		Methotrexate – subcut/IV	Placebo		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW
			n/N	n/N		
		Response: Clinical remission – 12wk*	8/60	2/51		
		Withdrawal: Withdrawal due to AEs – 12wk*	1/60	0/51		

Study & population	Arms	Outcomes			Limitations
complete withdrawal of steroids and no use of another immunosuppressive or anti-TNF therapy or colectomy.					Selective reporting: LOW Other bias: LOW Overall: LOW Indirectness: High Indirect treatment: only subcutaneous considered in evidence review.
		*Data obtained from study authors.			
Campieri et al. (2003)					
Extent: (1) Patients with left sided UC (%): 69/87 (79.3) Patients with extensive UC (%): 18/87 (20.7) (2) Patients with left sided UC (%): 58/90 (64.4) Patients with extensive UC (%): 32/90 (35.6) Extent classification: All (subgroups available) Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None reported	(1) N=80 Drug(s): standard-dose mesalazine - oral Dose: 2.4g (2) N=73 Drug(s): standard-dose beclomethasone - oral Dose: 5mg/day		standard-dose mesalazine - oral	standard-dose beclomethasone - oral	Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: HIGH (single blinded.) Detection bias: Blinding of outcome assessment: HIGH (single blinded.) Attrition bias: Incomplete outcome data: HIGH (>10% difference in missing data between the treatment arms) Selective reporting: LOW Other bias: LOW Overall: Remission: HIGH Withdrawal: MODERATE
			n/N	n/N	RR
		Withdrawal: Withdrawal due to AEs – 4wk	0/80	1/90	0.37 (CI: 0.02, 9.06)
		Extensive Response: Clinical remission – 4wk	9/18	19/26	0.68 (CI: 0.41, 1.15)
		Proctosigmoiditis/Left sided disease Response: Clinical remission – 4wk	41/62	27/47	1.15 (CI: 0.85, 1.56)

Study & population	Arms	Outcomes				Limitations
Definition of remission: DAI score <3						
Connolly et al. (2009) / Marteau 2005 / Probert 2014						
Extent: (1) All extensive (2) All extensive Extent classification: Extensive disease Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: UCDAI score < 2.	(1) N=47 Drug(s): high-dose mesalazine - oral Dose: 2g x2 a day. (2) N=58 Drug(s): high-dose mesalazine (oral) + mesalazine (topical) - oral asa and topical (liquid enema) asa Dose: 4g oral, 1g topical		high-dose mesalazine - oral	high-dose mesalazine (oral) + mesalazine (topical) - oral asa and topical (liquid enema) asa		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 2wk	16/53	21/63	0.91 (CI: 0.53, 1.55)	
		Clinical remission – 4wk	16/47	25/57	0.78 (CI: 0.47, 1.27)	
		Clinical remission – 8wk	20/47	37/58	0.67 (CI: 0.45, 0.98)	
		Withdrawal: Withdrawal due to AEs – 4wk	6/56	9/71	0.85 (CI: 0.32, 2.23)	
		Withdrawal due to AEs – 8wk	11/56	9/71	1.55 (CI: 0.69, 3.48)	
D'Haens et al. (2006)						
Extent: (1) left sided n=10, involvement of the transverse colon n=0, pancolitis n=2, missing n=1	(1) N=13 Drug(s): standard-dose mesalazine - oral Dose: 1.2g (2) N=14		standard-dose mesalazine (1.2g) - oral	high-dose mesalazine - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW
			n/N	n/N	RR	

Study & population	Arms	Outcomes				Limitations
(2) left sided n=11, involvement of the transverse colon n=0, pancolitis n=3, missing n=0 (3) left sided n=7, involvement of the transverse colon n=1, pancolitis n=3, missing n=0 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: Aminosalicylates and other (e.g. analgesics) Definition of remission: UCDAI score =1, with a score of 0 for rectal bleeding and stool frequency and at least a 1 point reduction from baseline in sigmoidoscopy score.	Drug(s): standard-dose mesalazine - oral Dose: 2.4g (3) N=11 Drug(s): high-dose mesalazine - oral Dose: 4.8g	Response: Clinical remission – 8wk	0/13	2/11	0.17 (CI: 0.01, 3.23)	Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: HIGH (>10% difference in missing data between groups) Selective reporting: LOW Other bias: LOW Overall: MODERATE
			standard-dose mesalazine (2.4g) - oral	high-dose mesalazine - oral		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	4/14	2/11	1.57 (CI: 0.35, 7.06)	

Study & population	Arms	Outcomes				Limitations
Dick A et al. (1964)						
Extent: (1) Colitis n=10, proctitis n=8 (2) Colitis n=17, proctitis n=6 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: Not reported Concomitant therapy: None reported Definition of remission: Remission not reported.	(1) N=21 Drug(s): standard-dose sulfasalazine - oral Dose: 4 to 6g (2) N=23 Drug(s): placebo		standard-dose sulfasalazine - oral	placebo		Selection bias HIGH (Potential for indirect population as some participants may not have active UC. The text reports: "the patients were either in an initial attack, in relapse after a remission, or were chronic cases in an exacerbation". Additionally, very limited baseline information) Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: UNCLEAR Overall: MODERATE
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 4wk	2/21	0/23	5.45 (CI: 0.28, 107.47)	
Feagan et al. (2013)						
Extent: (1) Proctitis n = 9, proctosigmoiditis n = 59, left-sided colitis n = 42, portion of	(1) N=140 Drug(s): high-dose mesalazine - oral Dose: 4.8g		high-dose mesalazine - oral	placebo		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW
			n/N	n/N	RR	

Study & population	Arms	Outcomes				Limitations
transverse colon n = 7, pancolitis n = 22, other n = 1 (2) Proctitis n = 3, proctosigmoiditis n = 68, left-sided colitis n = 51, portion of transverse colon n = 4, pancolitis n = 15, other n = 0 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None reported Definition of remission: A score of 0 for stool frequency and rectal bleeding, and absence of faecal urgency.	(2) N=141 Drug(s): placebo	Response: Clinical remission – 6wk	42/140	29/141	1.46 (CI: 0.97, 2.20)	Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: HIGH (84% completed trial in mesalazine group compared to 67% in placebo.) Selective reporting: LOW Other bias: LOW Overall: MODERATE
		Clinical remission – 10wk	57/140	30/141	1.91 (CI: 1.31, 2.78)	
		Withdrawal: Withdrawal due to AEs – 10wk	12/140	30/141	0.40 (CI: 0.22, 0.75)	
Feurle et al. (1989)						
Extent: (1) not provided (2) not provided	(1) N=52 Drug(s): standard-dose olsalazine - oral Dose: 2g		standard-dose olsalazine - oral	placebo	RR	Selection bias HIGH (Extent of disease and baseline information are not reported.) Random sequence generation: UNCLEAR

Study & population	Arms	Outcomes				Limitations
Extent classification: Not reported Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Not reported.	(2) N=53 Drug(s): placebo			n/N	n/N	Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: Detection bias: LOW Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: UNCLEAR Overall: MODERATE
		Withdrawal: Withdrawal due to AEs – 4wk		3/52	0/53	7.13 (CI: 0.38, 134.75)	
Gionchetti et al. (1998)							
Extent: (1) all proctitis (2) all proctitis Extent classification: Proctitis Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: DAI=0 on clinical section.	(1) N=29 Drug(s): standard-dose mesalazine - oral Dose: 2.4g (asacol) (2) N=29 Drug(s): standard-dose mesalazine - topical (suppository) Dose: 1.2g		standard-dose mesalazine - oral	standard-dose mesalazine - topical (suppository)		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: HIGH (single blind trial (investigator blind only)) Detection bias: Blinding of outcome assessment: LOW (Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: No upper limit to DAI score but means of scores are reflective of moderate UC.) Overall: MODERATE
			n/N	n/N	RR		
		Response: Clinical remission – 2wk	6/29	18/29	0.33 (CI: 0.15, 0.72)		
		Clinical remission – 4wk	12/29	26/29	0.46 (CI: 0.29, 0.72)		

Study & population	Arms	Outcomes				Limitations
Gross et al. (2006)						
Extent: (1) No % given. All proctitis or proctosigmoiditis (2) No % given. All proctitis or proctosigmoiditis Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: CAI = 4	(1) N=268 Drug(s): budesonidebudesonide - topical (foam) Dose: 2mg (2) N=264 Drug(s): budesonidebudesonide - topical (liquid enema) Dose: 2mg		budesonide - topical (foam)	topical (liquid enema)		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: UNCLEAR Incomplete outcome data: HIGH (>10% difference in missing data between groups.) Selective reporting: LOW Other bias: LOW (No upper limit on severity of population included, but mean and SD of severity measures are reflective of moderate UC.) Overall: MODERATE
			n/N	n/N	RR	
		Response: Clinical remission – 4wk	151/268	174/264	0.85 (CI: 0.75, 0.98)	
Gross et al. (2011)						
Extent: (1) subtotal/pancolitis n=32 (19%), left-sided colitis n=42 (25%), proctosigmoiditis n=92 (55%) (2) subtotal/pancolitis	(1) N=166 Drug(s): high-dose mesalazine - oral Dose: 3g (2) N=177 Drug(s): budesonidebudesonide - oral		high-dose mesalazine - oral	standard-dose budesonide - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW
			n/N	n/N	RR	
		Extensive Response: Clinical remission – 8wk	19/32	14/37	1.57 (CI: 0.95, 2.59)	

Study & population	Arms	Outcomes				Limitations
n=37 (21%), left-sided colitis n=42 (24%), proctosigmoiditis n=98 (55%) Extent classification: All (subgroups available) Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: CAI =4 with stool frequency <18/week and 0-1 bloody stool/week.	Dose: 9mg	Proctosigmoiditis/Left sided disease Response: Clinical remission – 8wk		72/134	56/140	1.34 (CI: 1.04, 1.74)	Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: UNCLEAR Overall: MODERATE
Hanauer (1998)							
Extent: (1) Not described – but all proctitis or proctosigmoiditis (2) Not described – but all proctitis or proctosigmoiditis (3) Not described – but all proctitis or proctosigmoiditis Extent classification:	(1) N=73 Drug(s): mesalazine - topical (liquid enema) Dose: 1g (2) N=70 Drug(s): placebo (3) N=71 Drug(s): mesalazine -		topical (liquid enema) n/N	placebo n/N	RR	Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR
		Response: Clinical remission – 8wk	32/73	10/70	3.07 (CI: 1.63, 5.76)	
			topical (liquid enema) n/N	placebo n/N	RR	

Study & population	Arms	Outcomes				Limitations
Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None reported Definition of remission: according to The number of bowel movements and the amount of blood in the stool.	topical (liquid enema) Dose: 2g (pentasa - 2g pentasa is not available in the UK, but this was included with the assumption that efficacy is the same or similar to 2g Salofalk, available in the UK).	Response: Clinical remission – 8wk	35/71	10/70	3.45 (CI: 1.86, 6.42)	Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
Hanauer et al. (1993)						
Extent: (1) - (2) Distal n=66 (68%), pancolitis n=31 (32%) (3) Distal n=68 (72%), pancolitis n=27 (28%) (4) Distal n=62 (69%), pancolitis n=28 (31%) Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate	(1) N=92 Drug(s): standard-dose mesalazine - oral Dose: 1g capsule (2) N=97 Drug(s): standard-dose mesalazine - oral Dose: 2g (3) N=95 Drug(s): high-dose		standard-dose mesalazine - oral (1g capsule)	high-dose mesalazine - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: HIGH (High discontinuation rate in placebo group.) Selective reporting: UNCLEAR Other bias: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	19/92	28/95	0.70 (CI: 0.42, 1.16)	
		Withdrawal: Withdrawal due to AEs – 8wk	5/92	7/95	0.74 (CI: 0.24, 2.24)	
			standard-dose mesalazine - oral (1g capsule)	placebo		
			n/N	n/N	RR	

Study & population	Arms	Outcomes				Limitations
Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Physician global assessment (PGA) of 1 - complete relief of symptoms.	mesalazine - oral Dose: 4g (4) N=90 Drug(s): placebo	Response: Clinical remission – 8wk	19/92	11/90	1.69 (CI: 0.85, 3.35)	Overall: MODERATE
		Withdrawal: Withdrawal due to AEs – 8wk	5/92	11/90	0.44 (CI: 0.16, 1.23)	
			standard-dose mesalazine - oral (2g)	high-dose mesalazine - oral		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	28/97	28/95	0.98 (CI: 0.63, 1.52)	
		Withdrawal: Withdrawal due to AEs – 8wk	9/97	7/95	1.26 (CI: 0.49, 3.24)	
			standard-dose mesalazine - oral (2g)	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	28/97	11/90	2.36 (CI: 1.25, 4.46)	
		Withdrawal: Withdrawal due to AEs – 8wk	9/97	11/90	0.76 (CI: 0.33, 1.75)	
			high-dose mesalazine - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	28/95	11/90	2.41 (CI: 1.28, 4.55)	

Study & population	Arms	Outcomes				Limitations
		Withdrawal: Withdrawal due to AEs – 8wk	7/95	11/90	0.60 (CI: 0.24, 1.49)	
Hanauer et al. (2005)						
Extent: (1) proctitis n=20, proctosigmoiditis n=49, left sided colitis n=42, pancolitis n=28 (2) proctitis n=21, proctosigmoiditis n=32, left sided colitis n=49, pancolitis n=27 Extent classification: Proctosigmoiditis and left sided Severity: moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Complete remission (used as 'clinical remission' not reported): complete resolution of: (i) stool frequency (normal stool frequency); (ii)	(1) N=139 Drug(s): standard-dose mesalazine - oral Dose: 2.4g (asacol) (2) N=129 Drug(s): high-dose mesalazine - oral Dose: 4.8g (asacol)		standard-dose mesalazine - oral n/N	high-dose mesalazine - oral n/N	 RR	Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: HIGH (> 10% difference in withdrawal between groups.) Selective reporting: LOW Other bias: LOW Overall: MODERATE
		Response: Clinical remission – 6wk	23/77	25/89	1.06 (CI: 0.66, 1.71)	
		Withdrawal: Withdrawal due to AEs – 6wk	4/139	4/129	0.93 (CI: 0.24, 3.63)	

Study & population	Arms	Outcomes				Limitations
rectal bleeding (no rectal bleeding); (iii) PFA score (generallywell); (iv) endoscopy findings (normal), and a PGA s						
Hanauer et al. (2007)						
Extent: (1) proctitis n=25, proctosigmoiditis n=45, left-side colitis n=45, pancolitis n=39 (2) proctitis n=29, proctosigmoiditis n=38, left-side colitis n=46, pancolitis n=34 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Complete remission not reported, only treatment success	(1) N=154 Drug(s): standard-dose mesalazine - oral Dose: 2.8g asacol (2) N=147 Drug(s): high-dose mesalazine - oral Dose: 4.8g asacol		standard-dose mesalazine - oral	high-dose mesalazine - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 6wk	8/154	5/147	1.53 (CI: 0.51, 4.56)	

Study & population	Arms	Outcomes				Limitations
(defined as clinical remission or clinical response)						
Hetzel et al. (1986)						
Extent: (1) No information given on % proctitis or left sided colitis (2) No information given on % proctitis or left sided colitis Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Not reported.	(1) N=15 Drug(s): standard-dose olsalazine - oral Dose: 2g (2) N=15 Drug(s): placebo		standard-dose olsalazine - oral	placebo		Selection bias Lack of baseline data - proportion of left-sided and proctitis not reported. Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: Overall: MODERATE
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 6wk	2/15	4/15	0.50 (CI: 0.11, 2.33)	
Irvine 2008 (ASCEND I and II)						
Extent: not reported Severity: mild-to-moderate Age: 18 - 75 years Concomitant therapy:	(1) N = 349 Drug: Mesalazine Dose: 2.4g (2) N = 338 Drug: Mesalazine Dose: 4.8g		Mean difference: standard-dose mesalazine – oral v High-dose mesalazine – oral			Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias:
			n/N			
		Quality of life (IBDQ) change from baseline to 6 weeks follow-up	-3.31 (-8.56, 1.95)			

Study & population	Arms	Outcomes				Limitations
						Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
Ito et al. (2010)						
Extent: (1) proctitis (n=24), others (n=42) (2) proctitis (n=24), others (n=40) (3) proctitis (n=25), others (n=38) (4) proctitis (n=11), others (n=21) Extent classification: Proctitis Severity: mild-to-moderate Age: 16 years and over Concomitant therapy: None reported Definition of remission: UCDAI of 2 or less and a	(1) N=66 Drug(s): standard-dose mesalazine - oral Dose: 2.4g asacol (2) N=64 Drug(s): standard-dose mesalazine - oral Dose: 3.6g asacol (3) N=63 Drug(s): standard-dose mesalazine - oral Dose: 2.25g pentasa (4) N=32		standard-dose mesalazine (2.4g asacol) - oral	placebo		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: MODERATE
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	20/66	3/32	3.23 (CI: 1.04, 10.08)	
		Withdrawal: Withdrawal due to AEs – 8wk	2/66	0/33	2.54 (CI: 0.13, 51.38)	
			standard-dose mesalazine (3.6g asacol) - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	29/64	3/32	4.83 (CI: 1.59, 14.67)	

Study & population	Arms	Outcomes				Limitations
bloody stool score of 0 at the final assessment.	Drug(s): placebo	Withdrawal: Withdrawal due to AEs – 8wk	1/65	0/33	1.55 (CI: 0.06, 36.93)	
			standard-dose mesalazine (2.25g pentasa) - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	18/63	3/32	3.05 (CI: 0.97, 9.58)	
		Withdrawal: Withdrawal due to AEs – 8wk	7/65	0/33	7.73 (CI: 0.45, 131.29)	
Jiang & (2004)						
Extent: (1) numbers not given (2) numbers not given Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission:	(1) N=21 Drug(s): standard-dose olsalazine - oral Dose: 2g/day (2) N=21 Drug(s): standard-dose sulfasalazine - oral Dose: 4g		standard-dose olsalazine - oral	high-dose sulfasalazine - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: HIGH (Unclear if blinded or open-label trial.) Detection bias: Blinding of outcome assessment: UNCLEAR Attrition bias: Incomplete outcome data: Selective reporting: UNCLEAROther bias: LOW Overall: HIGH
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	15/21	10/21	1.50 (CI: 0.89, 2.53)	

<table>
<tr><th>Study & population</th><th>Arms</th><th>Outcomes</th><th>Limitations</th></tr>
<tr><td>'Symptomatic clinical remission': defecation 0-2 times a day, with no gross blood or microscopic red cells in stool.</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">Kamm et al. (2007)</td></tr>
<tr><td>Extent:
(1) 70.2% left sided, 8.3% transverse, 21.4% pancolitis
(2) 78.8% left sided, 4.7% transverse, 16.5% pancolitis
(3) 80.2% left sided, 2.3% transverse, 17.4% pancolitis
(4) 73.3% left sided, 7.0% transverse, 19.8% pancolitis
Extent classification: Proctosigmoiditis and left sided
Severity: mild-to-moderate
Age: 18 years and over
Concomitant therapy: None permitted
Definition of remission: Modified UCDAI =1 with</td><td>(1) N=84
Drug(s): standard-dose mesalazine - oral
Dose: 2.4g (MMX)
(2) N=85
Drug(s): high-dose mesalazine - oral
Dose: 4.8g
(3) N=86
Drug(s): standard-dose mesalazine - oral
Dose: 2.4g (asacol)
(4) N=86
Drug(s): placebo</td><td><table>
<tr><td></td><td>standard-dose mesalazine (2.4g MMX) - oral</td><td>high-dose mesalazine - oral</td><td></td></tr>
<tr><td></td><td>n/N</td><td>n/N</td><td>RR</td></tr>
<tr><td>Response:
Clinical remission – 8wk</td><td>35/84</td><td>35/85</td><td>1.01 (CI: 0.71, 1.45)</td></tr>
<tr><td>Withdrawal:
Withdrawal due to AEs – 8wk</td><td>1/84</td><td>0/85</td><td>3.04 (CI: 0.13, 73.47)</td></tr>
</table>
<table>
<tr><td></td><td>standard-dose mesalazine (2.4g MMX) - oral</td><td>placebo</td><td></td></tr>
<tr><td></td><td>n/N</td><td>n/N</td><td>RR</td></tr>
<tr><td>Response:
Clinical remission – 8wk</td><td>35/84</td><td>19/86</td><td>1.89 (CI: 1.18, 3.02)</td></tr>
<tr><td>Withdrawal:
Withdrawal due to AEs – 8wk</td><td>1/84</td><td>2/86</td><td>0.51 (CI: 0.05, 5.54)</td></tr>
</table></td><td>Selection bias
Random sequence generation: UNCLEAR
Allocation concealment: LOW
Performance bias:
Blinding of participants/personnel: LOW
Detection bias:
Blinding of outcome assessment: LOW
Attrition bias:
Incomplete outcome data: LOW
Selective reporting:
LOW
Other bias:
LOW
Overall: LOW</td></tr>
</table>

Study & population	Arms	Outcomes				Limitations
rectal bleeding and stool frequency of 0, no mucosal friability and =1 point reduction in sigmoidoscopy score from baseline.			high-dose mesalazine - oral	standard-dose mesalazine (2.4g asacol) - oral		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	35/85	29/86	1.22 (CI: 0.83, 1.80)	
		Withdrawal: Withdrawal due to AEs – 8wk	0/85	1/86	0.34 (CI: 0.01, 8.16)	
			high-dose mesalazine - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	35/85	19/86	1.86 (CI: 1.16, 2.99)	
		Withdrawal: Withdrawal due to AEs – 8wk	0/85	2/86	0.20 (CI: 0.01, 4.15)	
			standard-dose mesalazine (2.4g asacol) - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	29/86	19/86	1.53 (CI: 0.93, 2.50)	
		Withdrawal: Withdrawal due to AEs – 8wk	1/86	2/86	0.50 (CI: 0.05, 5.41)	

<table>
<tr><th>Study & population</th><th>Arms</th><th>Outcomes</th><th>Limitations</th></tr>
<tr><td>Kruis et al. (2003)</td><td></td><td></td><td></td></tr>
<tr><td>Extent:
(1) 57% Proctosigmoiditis, 26% left-sided, 16% subtotal/total, 1% unknown
(2) 37% Proctosigmoiditis, 41% left-sided, 21% subtotal/total, 1% unknown
(3) 44% Proctosigmoiditis, 33% left-sided, 23% subtotal/total, 0% unknown
Extent classification: Proctosigmoiditis and left sided
Severity: mild-to-moderate
Age: 18 years and over
Concomitant therapy: None permitted
Definition of remission: Clinical activity index equal to or less than 4.</td><td>(1) N=103
Drug(s): standard-dose mesalazine - oral
Dose: 1.5g
(2) N=107
Drug(s): high-dose mesalazine - oral
Dose: 3g
(3) N=106
Drug(s): high-dose mesalazine - oral
Dose: 4.5g</td><td><table>
<tr><td></td><td>standard-dose mesalazine - oral</td><td>high-dose mesalazine (3g) - oral</td><td></td></tr>
<tr><td></td><td>n/N</td><td>n/N</td><td>RR</td></tr>
<tr><td>Response: Clinical remission – 8wk</td><td>52/103</td><td>71/107</td><td>0.76 (CI: 0.60, 0.96)</td></tr>
<tr><td></td><td>standard-dose mesalazine - oral</td><td>high-dose mesalazine (4.5g) - oral</td><td></td></tr>
<tr><td></td><td>n/N</td><td>n/N</td><td>RR</td></tr>
<tr><td>Response: Clinical remission – 8wk</td><td>52/103</td><td>58/106</td><td>0.92 (CI: 0.71, 1.19)</td></tr>
</table></td><td>Selection bias
Random sequence generation: UNCLEAR
Allocation concealment: UNCLEAR
Performance bias:
Blinding of participants/personnel: LOW
Detection bias:
Blinding of outcome assessment: LOW
Attrition bias:
Incomplete outcome data: HIGH
Selective reporting:
UNCLEAR
Other bias:
Overall: MODERATE</td></tr>
<tr><td>Lauritsen et al. (1986)</td><td></td><td></td><td></td></tr>
</table>

Study & population	Arms	Outcomes				Limitations
Extent: (1) numbers not given (2) numbers not given Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: SASP Definition of remission: Not described.	(1) N=13 Drug(s): mesalazine - topical (liquid enema) Dose: 1g (2) N=11 Drug(s): prednisolone - topical (liquid enema) Dose: 25mg		mesalazine - topical (liquid enema)	prednisolone - topical (liquid enema)		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: HIGH Incomplete outcome data: LOW Selective reporting: UNCLEAR Other bias: LOW Overall: MODERATE
			n/N	n/N	RR	
		Response: Clinical remission – 4wk	7/13	9/11	0.66 (CI: 0.37, 1.17)	
Lawrance et al. (2017)						
Extent classification: Proctitis Severity: moderate Age: 18 years and over Concomitant therapy: Immunomodulators and/or oral/topical ASA/steroid Definition of remission: Mayo Clinical score =< 2 and no subscore >	(1) N=11 Drug(s): tacrolimus - topical (ointment) Dose: 0.5 mg/mL (2) N=10 Drug(s): placebo		tacrolimus - topical (ointment)	placebo		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: UNCLEAR Other bias:
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	5/11	0/10	10.08 (CI: 0.63, 162.06)	

Study & population	Arms	Outcomes				Limitations
1 and mucosal healing, defined as an endoscopic subscore of 0 or 1.						LOW Indirectness – indirect treatment preparation (ointment) Overall: LOW
Lennard-Jones et al. (1960)						
Extent: (1) numbers not given (2) numbers not given Extent classification: Extensive disease Severity: mild Age: 18 years and over Concomitant therapy: None reported Definition of remission: Freedom from symptoms combined with the finding of an inactive or, rarely, normal mucosa on sigmoidoscopy.	(1) N=20 Drug(s): standard-dose sulfasalazine - oral Dose: 4g in total (detail regarding regimen not provided) (2) N=19 Drug(s): prednisolone - oral Dose: 40 to 60mg		standard-dose sulfasalazine - oral	prednisolone - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 4wk	8/20	11/20	0.73 (CI: 0.37, 1.42)	
Levine et al. (2002)						
Extent: (1) <60cm n=15, >60cm n=34 (2) <60cm n=15, >60cm n=34	(1) N=36 Drug(s): standard-dose mesalazine - oral		standard-dose mesalazine - oral	standard-dose balsalazide - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias:
			n/N	n/N	RR	

Study & population	Arms	Outcomes				Limitations
(3) <60cm n=15, >60cm n=34 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Complete remission (used as 'clinical remission' not reported): no rectal bleeding, normal stool frequency, a sigmoidoscopicscore of normal or mild and a Physician's Global Assessment score of quiescent disease activity.	Dose: 2.4g asacol (2) N=35 Drug(s): standard-dose balsalazide - oral Dose: 2.25g (3) N=35 Drug(s): high-dose balsalazide - oral Dose: 6.67g	Response: Clinical remission – 8wk	7/36	7/35	0.97 (CI: 0.38, 2.49)	Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: HIGH (High dropout rate across groups.) Selective reporting: UNCLEAR Other bias: Overall: MODERATE
		Withdrawal: Withdrawal due to AEs – 8wk	5/51	5/50	0.98 (CI: 0.30, 3.18)	
			standard-dose mesalazine - oral	high-dose balsalazide - oral		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	7/36	8/35	0.85 (CI: 0.35, 2.10)	
		Withdrawal: Withdrawal due to AEs – 8wk	5/51	1/53	5.20 (CI: 0.63, 42.96)	
			standard-dose balsalazide - oral	high-dose balsalazide - oral		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	7/35	8/35	0.88 (CI: 0.36, 2.15)	
		Withdrawal: Withdrawal due to AEs – 8wk	5/50	1/53	5.30 (CI: 0.64, 43.80)	
Lichtenstein et al. (2007)						
Extent: (1) left sided n=71 (79.8%), involvement of the transverse n=6 (6.7%), pancolitis n=11 (12.4%)	(1) N=88 Drug(s): standard-dose mesalazine - oral Dose: 2.4g MMX		standard-dose mesalazine - oral	high-dose mesalazine - oral		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW
			n/N	n/N	RR	

Study & population	Arms	Outcomes				Limitations
(2) left sided n=78 (88.6%), involvement of the transverse n=4 (4.5%), pancolitis n=6 (6.8%) (3) left sided n=66 (77.6%), involvement of the transverse n=4 (4.7%), pancolitis n=15 (17.6%) Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: Aminosalicylates and other (e.g. analgesics) Definition of remission: Modified UCDAI score of =1, with a score of 0 for rectal bleeding and stool frequency, and at least a 1 point reduction in sigmoidoscopy score.	(2) N=89 Drug(s): high-dose mesalazine - oral Dose: 4.8g (3) N=85 Drug(s): placebo	Response: Clinical remission	33/88	29/89	1.15 (CI: 0.77, 1.72)	Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
		Withdrawal: Withdrawal due to adverse events	5/88	2/89	2.53 (CI: 0.50, 12.69)	
			standard-dose mesalazine - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission	33/88	16/85	1.99 (CI: 1.19, 3.34)	
		Withdrawal: Withdrawal due to adverse events	5/88	11/85	0.44 (CI: 0.16, 1.21)	
			high-dose mesalazine - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission	29/89	16/85	1.73 (CI: 1.02, 2.95)	
		Withdrawal: Withdrawal due to adverse events	2/89	11/85	0.17 (CI: 0.04, 0.76)	

Study & population	Arms	Outcomes				Limitations
Naganuma et al. (2016)						
Extent: (1) proctitis n = 26, sigmoiditis n = 29 (2) proctitis n = 28, sigmoiditis n = 28 (3) proctitis n = 25, sigmoiditis n = 29 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 16 years and over Concomitant therapy: Mesalazine or SASP permitted Definition of remission: Rectal bleeding subscore of 0 and endoscopic subscore = 1, and a stool frequency subscore of 0.	(1) N=55 Drug(s): budesonide - topical (foam) Dose: 2mg once a day (2) N=56 Drug(s): standard-dose budesonide - topical (foam) Dose: 4mg (2mg twice a day) (3) N=54 Drug(s): placebo		budesonide (od) - topical (foam)	budesonide (bd) - topical (foam)		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 6wk	28/55	27/56	1.06 (CI: 0.73, 1.54)	
		Withdrawal: Withdrawal due to AEs – 6wk	0/55	2/56	0.20 (CI: 0.01, 4.15)	
			standard-dose budesonide (od) - topical (foam)	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 6wk	28/55	11/54	2.50 (CI: 1.39, 4.50)	
		Withdrawal: Withdrawal due to AEs – 6wk	0/55	2/54	0.20 (CI: 0.01, 4.00)	
			standard-dose budesonide (bd) - topical (foam)	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 6wk	27/56	11/54	2.37 (CI: 1.31, 4.28)	
		Withdrawal: Withdrawal due to AEs – 6wk	2/56	2/54	0.96 (CI: 0.14, 6.60)	
Naganuma et al. (2017)						

Study & population	Arms	Outcomes				Limitations
Extent: (1) pancolitis n = 11, left-sided n = 31, proctitis n = 22 (2) pancolitis n = 5, left-sided n = 34, proctitis n = 23 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 16 years and over Concomitant therapy: Mesalazine or SASP permitted Definition of remission: The percentage of patients with a rectal bleeding subscore of 0, endoscopic subscore of 0 or 1, and stool frequency subscore of 0 or a decrease in this subscore by at least 1 from baseline.	(1) N=64 Drug(s): budesonide - topical (foam) Dose: 2mg (2) N=62 Drug(s): placebo		budesonide - topical (foam)	placebo		Selection bias Random sequence generation: UNCLEAR Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 6wk	26/64	10/62	2.52 (CI: 1.33, 4.78)	
		Withdrawal: Withdrawal due to AEs – 6wk	4/64	2/62	1.94 (CI: 0.37, 10.20)	
Ogata et al. (2017)						

Study & population	Arms	Outcomes				Limitations
Extent: (1) proctitis n = 51, left-sided n = 65, pancolitis n = 22, segmental n = 1 (2) proctitis n = 56, left-sided n = 65, pancolitis n = 16, segmental n = 2 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 16 years and over Concomitant therapy: None reported Definition of remission: Rectal bleeding score=0 and stool frequency score=0.	(1) N=136 Drug(s): high-dose mesalazine - oral Dose: 4.8g MMX (2) N=131 Drug(s): standard-dose mesalazine - oral Dose: 3.6g MMX		high-dose mesalazine - oral	standard-dose mesalazine - oral		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	56/136	40/131	1.35 (CI: 0.97, 1.87)	
		Withdrawal: Withdrawal due to AEs – 8wk	8/140	17/140	0.47 (CI: 0.21, 1.05)	
Ogata et al (2018)						
Extent: (1) proctitis n = 29, left-sided n = 38, pancolitis n = 15, segmental n = 3 (2) proctitis n = 28, left-sided n = 40, pancolitis n = 17, segmental n = 0	(1) N= 85 Drug(s): mesalazine Dose: 2.25g (2) N= 85 Drug(s): mesalazine		standard-dose mesalazine – oral	standard-dose mesalazine – oral	high-dose mesalazine – oral	Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias:
			n/N	n/N	n/N	
		Response: Clinical remission – 8wk	24/85	27/85	37/81	

Study & population	Arms	Outcomes				Limitations
(3) proctitis n = 33, left-sided n = 38, pancolitis n = 7, segmental n = 3 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 16 years and over Concomitant therapy: None Definition of remission: UCDAI score ≤2 and rectal bleeding score=0 at the end of the treatment period).	Dose: 2.4g MMX (3) N = 81 Drug(s) mesalazine Dose: 4.8g MMX	Withdrawal: Withdrawal due to AEs – 8wk	6/85	9/85	7/81	Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
Pokrotnieks et al. (2000)						
Extent: (1) proctitis n=13, proctosigmoiditis n=31, left sided UC n=10 (2) proctitis n=20, proctosigmoiditis n=29, left sided UC n=8 Extent classification: All (subgroups available)	(1) N=54 Drug(s): topical (foam) Dose: 2g Salofalk (not available in the UK, assumed similar efficacy to 2x 1g Salofalk) (2) N=57 Drug(s): placebo		mesalazine - topical (foam) n/N	placebo n/N	 RR	Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR
		Proctitis Response: Clinical remission – 6wk	7/13	8/20	1.35 (CI: 0.64, 2.81)	
		Proctosigmoiditis/Left sided disease Response: Clinical remission – 6wk	23/41	13/37	1.60 (CI: 0.95, 2.67)	

Study & population	Arms	Outcomes				Limitations
Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: - Definition of remission: CAI =< 4.		Withdrawal: Withdrawal due to AEs – 6wk	1/54	1/57	1.06 (CI: 0.07, 16.46)	Other bias: LOW Overall: LOW
Pontes et al. (2014)						
Extent: 20cm or more from the rectum. Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Clinical remission: stool frequency and rectal bleeding subscores =<1.	(1) N=8 Drug(s): standard-dose mesalazine - oral Dose: 2.4g (2) N=13 Drug(s): placebo		standard-dose mesalazine - oral	placebo		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 4wk	1/8	1/13	1.63 (CI: 0.12, 22.50)	
Pruitt et al. (2002)						

Study & population	Arms	Outcomes				Limitations
Extent: (1) ≤40cm n=45, > 40cm n=39 (2) ≤40cm n=49, > 40cm n=40 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 12 years and over Concomitant therapy: None permitted Definition of remission: PFA score of normal or mild and absence of rectal bleeding.	(1) N=73 Drug(s): high-dose balsalazide - oral Dose: 6.75 (2) N=77 Drug(s): standard-dose mesalazine - oral Dose: 2.4g (asacol)		high-dose balsalazide - oral	standard-dose mesalazine - oral		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: UNCLEAR Other bias: UNCLEAR Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	38/73	38/77	1.05 (CI: 0.77, 1.45)	
		Withdrawal: Withdrawal due to AEs – 8wk	3/84	6/89	0.53 (CI: 0.14, 2.05)	
Rizzello et al. (2002)						
Extent: (1) Left sided (%): 38/58 (66) Pancolitis (%): 20/58 (34) (2) Mild (%): 14/58 (24) Moderate (%): 44/58 (76) Extent classification:	(1) N=58 Drug(s): standard-dose mesalazine and beclomethasone - oral asa + oral corticosteroid Dose: 3.2g asacol and 5mg beclomethasone (2) N=61		standard-dose mesalazine and beclomethasone - oral asa + oral corticosteroid	standard-dose mesalazine - oral		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias:
			n/N	n/N	RR	
		Response: Clinical remission – 4wk	34/58	21/61	1.70 (CI: 1.13, 2.56)	
		Withdrawal: Withdrawal due to AEs – 4wk	1/58	3/61	0.35 (CI: 0.04, 3.27)	

<table>
<tr><th>Study & population</th><th>Arms</th><th>Outcomes</th><th>Limitations</th></tr>
<tr><td>Proctosigmoiditis and left sided
Severity: mild-to-moderate
Age: 18 years and over
Concomitant therapy: None permitted
Definition of remission: DAI score <3</td><td>Drug(s): standard-dose mesalazine - oral
Dose: 3.2g asacol</td><td></td><td>Incomplete outcome data: HIGH (>10% difference in withdrawals between groups.)
Selective reporting:
UNCLEAR
Other bias: LOW
Overall: MODERATE</td></tr>
<tr><td colspan="4">Romano et al. (2010)</td></tr>
<tr><td>Extent:
(1) Pancolitis (%): 5/15 (33.3)
Left sided (%): 10/15 (66.7)
(2) Pancolitis (%): 9/15 (60)
Left sided (%): 6/15 (40)
Extent classification: Extensive disease
Severity: mild-to-moderate
Age: 5 - 17 years
Concomitant therapy: None reported
Definition of remission: PUCAI score < 10</td><td>(1) N=15
Drug(s): high-dose mesalazine - oral
Dose: 80mg/kg/day
(2) N=15
Drug(s): standard-dose beclomethasone - oral
Dose: 5mg</td><td><table><tr><td></td><td>high-dose mesalazine - oral</td><td>standard-dose beclomethasone - oral</td><td></td></tr><tr><td></td><td>n/N</td><td>n/N</td><td>RR</td></tr><tr><td>Response:
Clinical remission – 4wk</td><td>5/15</td><td>12/15</td><td>0.42 (CI: 0.20, 0.89)</td></tr></table></td><td>Selection bias
Random sequence generation: UNCLEAR
Allocation concealment: UNCLEAR
Performance bias:
Blinding of participants/personnel: HIGH (Open-label study.)
Detection bias:
Blinding of outcome assessment: HIGH
Attrition bias:
Incomplete outcome data:
Selective reporting:
HIGH (Open-label study.)
Other bias:
LOW
Overall: HIGH</td></tr>
</table>

Study & population	Arms	Outcomes				Limitations
Rubin et al. (2017)						
Extent: (1) proctosigmoiditis n=94, left-sided n=84, extensive n = 13, pancolitis n=39 (2) proctosigmoiditis n=85, left-sided n=94, extensive n = 16, pancolitis n=33 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: Mesalazine Definition of remission: UCDAI subscale scores of 0 for rectal bleeding and stool frequency.	(1) N=230 Drug(s): budesonidebudesonide - oral Dose: 9mg MMX (2) N=228 Drug(s): placebo		budesonide - oral	placebo		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: HIGH (>10% difference in missing data between groups.) Selective reporting: LOW Other bias: LOW Overall: MODERATE
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	56/230	52/228	1.07 (CI: 0.77, 1.48)	
		Withdrawal: Withdrawal due to AEs – 8wk	12/255	9/255	1.33 (CI: 0.57, 3.11)	
Sandborn et al. (2009)						
Extent: (1) proctosigmoiditis n=183, left-sided n=136, pancolitis n=60 (2) proctosigmoiditis n=185, left-sided	(1) N=359 Drug(s): standard-dose mesalazine - oral Dose: 2.4g (asacol) (2) N=365		standard-dose mesalazine - oral	high-dose mesalazine - oral		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias:
			n/N	n/N	RR	
		Response: Clinical remission – 3wk	65/359	91/365	0.73 (CI: 0.55, 0.96)	

Study & population	Arms	Outcomes				Limitations
n=138, pancolitis n=61 Extent classification: Proctosigmoiditis and left sided Severity: moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: PGA score = 0 i.e. complete resolution of or normalization of stool frequency, bleeding and sigmoidoscopy with CFT assessment score.	Drug(s): high-dose mesalazine - oral Dose: 4.8g (asacol)	Clinical remission – 6wk	121/347	152/353	0.81 (CI: 0.67, 0.98)	Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
		Withdrawal: Withdrawal due to AEs – 6wk	15/383	15/389	1.02 (CI: 0.50, 2.05)	
Sandborn et al. (2012)						
Extent: (1) proctosigmoiditis n=37, left sided colitis n=35, extensive/ pancolitis n=52 (2) proctosigmoiditis n=41, left sided colitis n=34, extensive/ pancolitis n=40, missing n=6	(1) N=124 Drug(s): standard-dose mesalazine - oral Dose: 2.4g asacol (2) N=123 Drug(s): budesonidebudesonide - oral		standard-dose mesalazine - oral n/N	budesonide - oral n/N	RR	Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias:
		Response: Clinical remission – 8wk	15/124	22/123	0.68 (CI: 0.37, 1.24)	
		Withdrawal: Withdrawal due to AEs – 8wk	14/124	15/127	0.96 (CI: 0.48, 1.90)	

Study & population	Arms	Outcomes				Limitations
Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None reported Definition of remission: UCDAI score =< 1 point, with subscores of 0 for both rectal bleeding and stool frequency (based on the 3 days closest to the week 8 visit with nonmissing diary data within a 5-day window closest to the visit [the 5 days did not include any days on which a	Dose: 9mg MMX (3) N=121 Drug(s): placebo		standard-dose mesalazine - oral	placebo		Incomplete outcome data: HIGH (>10% difference in withdrawal rate in placebo group.) Selective reporting: LOW Other bias: LOW Overall: MODERATE
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	15/124	9/121	1.63 (CI: 0.74, 3.57)	
		Withdrawal: Withdrawal due to AEs – 8wk	14/124	24/129	0.61 (CI: 0.33, 1.12)	
			budesonide - oral	placebo		
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	22/123	9/121	2.40 (CI: 1.15, 5.01)	
		Withdrawal: Withdrawal due to AEs – 8wk	15/127	24/129	0.63 (CI: 0.35, 1.15)	
Sandborn et al. (2015)						
Extent: (1) proctitis n = 72, proctosigmoiditis n=193, missing n = 2 (1) proctitis n = 81, proctosigmoiditis	(1) N=267 Drug(s): budesonide - topical (foam) Dose: 2mg (2) N=279 Drug(s): placebo		budesonide - topical (foam)	placebo		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW
			n/N	n/N	RR	

Study & population	Arms	Outcomes				Limitations
n=197, missing n = 1 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: Mesalazine Definition of remission: 'Remission' endoscopy subscore<=<1, rectal bleeding subscore of 0, and improvement or no change from baseline in the stool frequency subscore of the Mayo score. The outcome 'clinical remission' was not reported, but 'remission' was viewed to be directly a		Response: Clinical remission – 6wk	110/267	67/279	1.72 (CI: 1.33, 2.21)	Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: LOW Other bias: LOW Overall: MODERATE
		Withdrawal: Withdrawal due to AEs – 6wk	26/268	12/278	2.25 (CI: 1.16, 4.36)	
Scherl et al. (2009)						
Extent: (1) No data on extent of disease given at baseline.	(1) N=166 Drug(s): high-dose		high-dose balsalazide - oral	placebo	RR	Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias:

Study & population	Arms	Outcomes				Limitations
(2) No data on extent of disease given at baseline. Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None reported Definition of remission: Score of 0 for rectal bleeding and a combined score of =2 for bowel frequency and physician's assessment using the MMDAI subscales at week 8/ end of treatment.	balsalazide - oral Dose: 6.6g (1.1g x3 twice a day) (2) N=83 Drug(s): placebo		n/N	n/N		Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
		Response: Clinical remission – 8wk	64/166	19/83	1.68 (CI: 1.09, 2.61)	
		Withdrawal: Withdrawal due to AEs – 8wk	15/166	10/83	0.75 (CI: 0.35, 1.60)	
Schroeder et al. (1987)						
Extent: (1) Universal colitis n=0 (0%), left-sided colitis n=11 (100%), rectal sparing n=0 (0%) (2) Universal colitis n=10 (26%), left-sided colitis n=28	(1) N=11 Drug(s): standard-dose mesalazine - oral Dose: 1.6g asacol (2) N=38		standard-dose mesalazine - oral	high-dose mesalazine - oral		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias:
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 6wk	1/11	1/38	3.45 (CI: 0.23, 50.86)	

Study & population	Arms	Outcomes				Limitations
(74%), rectal sparing n=2 (5%) (3) Universal colitis n=10 (26%), left-sided colitis n=28 (74%), rectal sparing n=3 (8%) Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: -	Drug(s): high-dose mesalazine - oral Dose: 4.8g asacol (3) N=38 Drug(s): placebo		standard-dose mesalazine - oral	placebo		Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 6wk	1/11	2/38	1.73 (CI: 0.17, 17.31)	
			high-dose mesalazine - oral	placebo		
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 6wk	1/38	2/38	0.50 (CI: 0.05, 5.28)	
Sninsky et al. (1991)						
Extent: (1) >40cm N=20, 20-40cm N=25, <20cm N=8 (2) >40cm N=24, 20-40cm N=20, <20cm N=9 (3) >40cm N=17, 20-40cm N=25, <20cm N=10 Extent classification: Proctosigmoiditis and left sided	(1) N=53 Drug(s): standard-dose mesalazine - oral Dose: 1.6g asacol (2) N=53 Drug(s): standard-dose mesalazine - oral Dose: 2.4g asacol		standard-dose mesalazine (1.6g) - oral	placebo		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR
			n/N	n/N	RR	
		Response: Clinical remission – 3wk	1/53	1/52	0.98 (CI: 0.06, 15.28)	
		Clinical remission – 6wk	6/53	2/52	2.94 (CI: 0.62, 13.92)	
		Withdrawal: Withdrawal due to AEs – 6wk	0/53	0/52		

Study & population	Arms	Outcomes				Limitations
Severity: mild-to-moderate Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Complete resolution of all symptoms, with all assessment scores determined to be zero.	(3) N=52 Drug(s): placebo		standard-dose mesalazine (2.4g) - oral	placebo		Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 3wk	1/53	1/52	0.98 (CI: 0.06, 15.28)	
		Clinical remission – 6wk	6/53	2/52	2.94 (CI: 0.62, 13.92)	
		Withdrawal: Withdrawal due to AEs – 6wk	2/53	0/52	4.91 (CI: 0.24, 99.82)	
Suzuki et al. (2016)						
Extent: (1) ulcerative proctitis n = 11, left-sided colitis n = 28, right sided or segmental colitis n = 2, extensive n = 14 (2) ulcerative proctitis n = 9, left-sided colitis n = 26, right sided or segmental colitis n = 1, extensive n = 19 Extent classification: Proctosigmoiditis and left sided	(1) N=55 Drug(s): standard-dose mesalazine - oral Dose: 3.6g (asacol) (2) N=55 Drug(s): high-dose mesalazine - oral Dose: 4.8		standard-dose mesalazine - oral	high-dose mesalazine - oral		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 8wk	10/55	14/55	0.71 (CI: 0.35, 1.47)	
		Withdrawal: Withdrawal due to AEs – 8wk	1/55	1/55	1.00 (CI: 0.06, 15.59)	

Study & population	Arms	Outcomes				Limitations
Severity: mild-to-moderate Age: 16 years and over Concomitant therapy: None permitted Definition of remission: UCDAI =2 and a rectal-bleeding score of 0.						
Travis et al. (2013)						
Extent: (1) proctosigmoiditis n=58, left sided colitis n=37, extensive/pancolitis n = 31 (2) proctosigmoiditis n=51, left sided colitis n=49, extensive/pancolitis n = 26 (3) proctosigmoiditis n=64, left sided colitis n=44, extensive/pancolitis n = 20 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate	(1) N=128 Drug(s): budesonide - oral Dose: 9mg MMX (2) N=126 Drug(s): budesonide - oral Dose: 9mg entocort (3) N=129 Drug(s): placebo		budesonide (MMX) - oral	placebo		Selection bias Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: LOW Selective reporting: LOW Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 8wk	24/128	19/129	1.27 (CI: 0.73, 2.21)	
			budesonide (entocort) - oral	placebo		
			n/N	n/N	RR	
		Withdrawal: Withdrawal due to AEs – 8wk	22/126	19/129	1.19 (CI: 0.68, 2.08)	
		Additional data was available for budesonide 6mg - this was not included as it is unavailable in the UK.				

Study & population	Arms	Outcomes				Limitations
Age: 18 years and over Concomitant therapy: None permitted Definition of remission: Not reported.						
Vecchi et al. (2001)						
Extent: (1) proctosigmoiditis n=33, left colon n=17, ascending + transverse n=17 (2) proctosigmoiditis n=43, left colon n=17, ascending + transverse n=3 Extent classification: Proctosigmoiditis and left sided Severity: mild-to-moderate Age: 21 years and over Concomitant therapy: None reported Definition of remission: Clinical Activity Index < 4.	(1) N=67 Drug(s): standard-dose mesalazine - oral Dose: 2g (2) N=63 Drug(s): standard-dose mesalazine (oral) + mesalazine (topical) - oral asa and topical (liquid enema) asa Dose: 2g + 2g		standard-dose mesalazine - oral	standard-dose mesalazine (oral) + mesalazine (topical) - oral asa and topical (liquid enema) asa		Selection bias Random sequence generation: LOW Allocation concealment: LOW Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 6wk	55/67	55/63	0.94 (CI: 0.81, 1.09)	
Watanabe et al. (2013)						

Study & population	Arms	Outcomes				Limitations
Extent: (1) pancolitis n = 11, left-sided n = 4, sigmoiditis n = 13, proctitis n = 37 (2) pancolitis n = 7, left-sided n = 7, sigmoiditis n = 14, proctitis n = 36 Extent classification: Proctitis Severity: mild-to-moderate Age: 15 years and over Concomitant therapy: Mesalazine Definition of remission: UC-DAI scores of 2 or less and a bleeding score of 0.	(1) N=65 Drug(s): mesalazine - topical (suppository) Dose: 1g (2) N=64 Drug(s): placebo		mesalazine - topical (suppository)	placebo		Selection bias Random sequence generation: LOW Allocation concealment: UNCLEAR Performance bias: Blinding of participants/personnel: LOW Detection bias: Blinding of outcome assessment: LOW Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: LOW
			n/N	n/N	RR	
		Response: Clinical remission – 4wk	41/65	11/64	3.67 (CI: 2.08, 6.48)	
		Withdrawal: Withdrawal due to AEs – 4wk	0/65	2/64	0.20 (CI: 0.01, 4.02)	
Winter et al. (2014)						
Extent: (1) pancolitis n = 10, extensive n = 3, left-sided n = 10, proctosigmoiditis n = 7, proctitis n = 3, missing n = 8 (2) pancolitis n = 17, extensive n = 4, left-sided n = 6, proctosigmoiditis n	(1) N=41 Drug(s): standard-dose mesalazine - oral Dose: 27 to 71 mg/g/day (2) N=40 Drug(s): high-dose		standard-dose mesalazine - oral	high-dose mesalazine - oral		Selection bias UNCLEAR (Difference at baseline: more people had pancolitis in high dose group (42% vs 24% in low dose). Random sequence generation: UNCLEAR Allocation concealment: UNCLEAR Performance bias:
			n/N	n/N	RR	
		Response: Clinical remission – 6wk	19/41	17/40	1.09 (CI: 0.67, 1.78)	

Study & population	Arms	Outcomes				Limitations
= 4, proctitis n = 5, missing n = 5 Extent classification: Extensive disease Severity: mild-to-moderate Age: 5 - 17 years Concomitant therapy: None permitted Definition of remission: PUCAI score <10.	mesalazine - oral Dose: 53 - 118 mg/g/day	Withdrawal: Withdrawal due to AEs – 6wk	5/41	2/41	2.50 (CI: 0.51, 12.16)	Blinding of participants/personnel: LOW Detection bias: UNCLEAR Blinding of outcome assessment: Attrition bias: Incomplete outcome data: UNCLEAR Selective reporting: UNCLEAR Other bias: LOW Overall: MODERATE

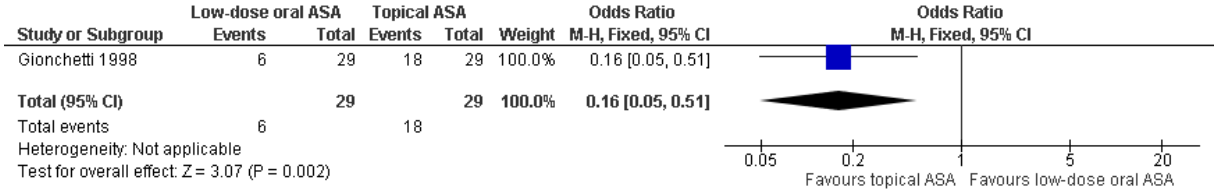
Appendix G: Forest plots - pairwise meta-analysis

G.1 Clinical remission

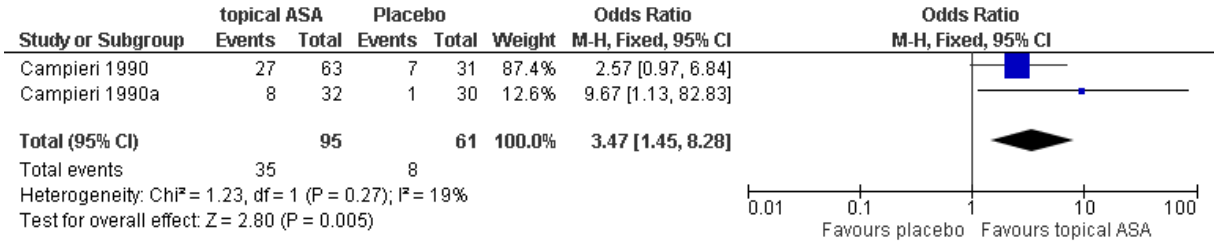
G.1.1 Proctitis

2 weeks follow-up

Low-dose oral ASA v topical ASA

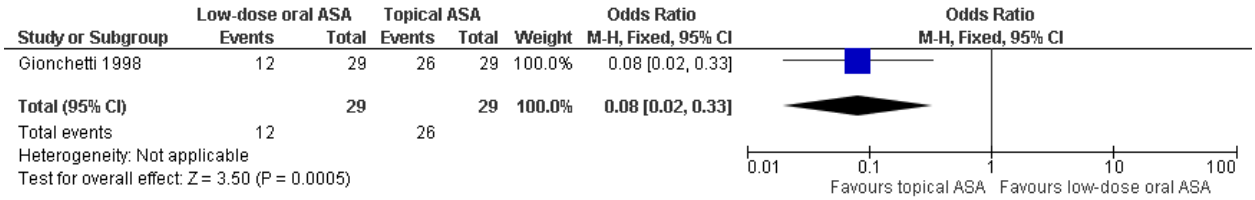


Topical ASA v placebo

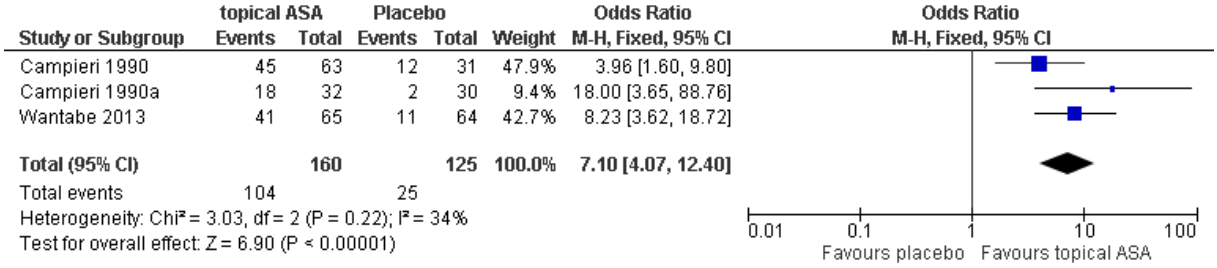


3 to 4 weeks follow-up

Low-dose oral ASA v topical ASA

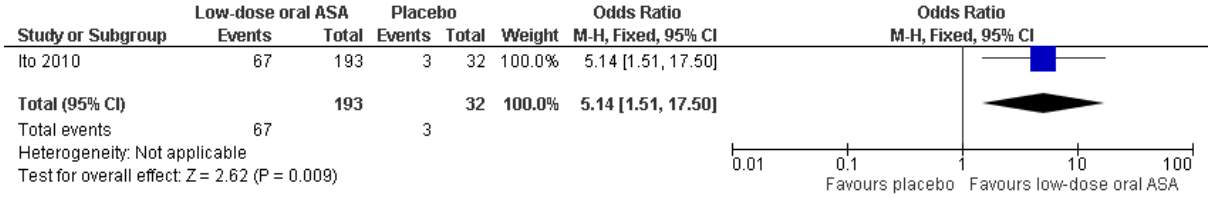


Topical ASA v placebo

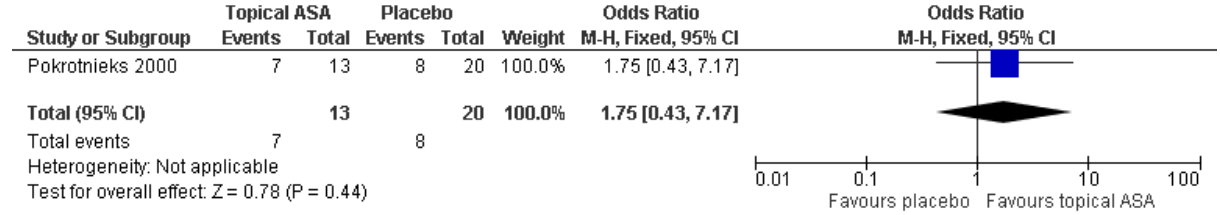


5 to 8 weeks follow-up

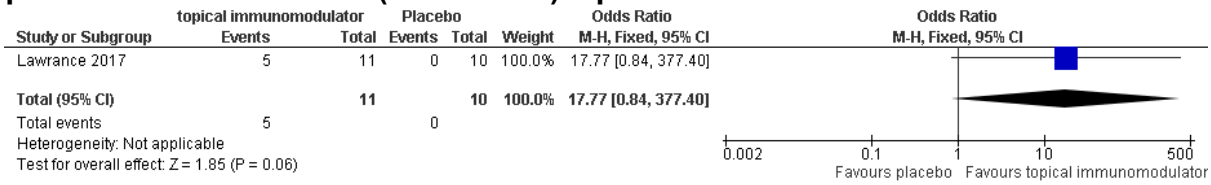
Low-dose oral ASA v placebo



Topical ASA v placebo



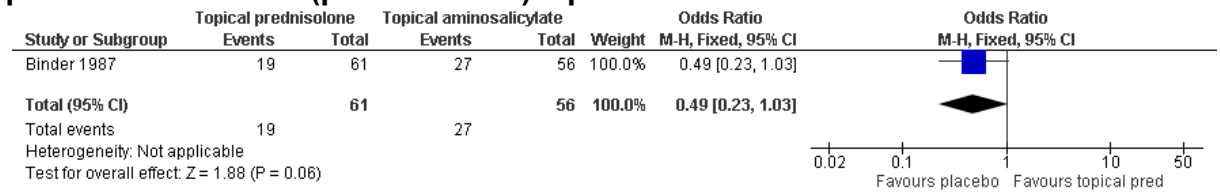
Topical immunomodulator (tacrolimus) v placebo



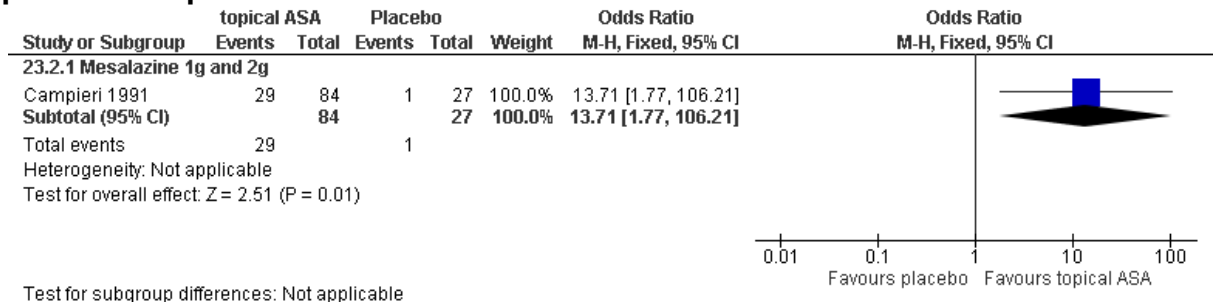
G.2 Proctosigmoiditis and left-sided

2 weeks follow-up

Topical corticosteroid (prednisolone) v placebo

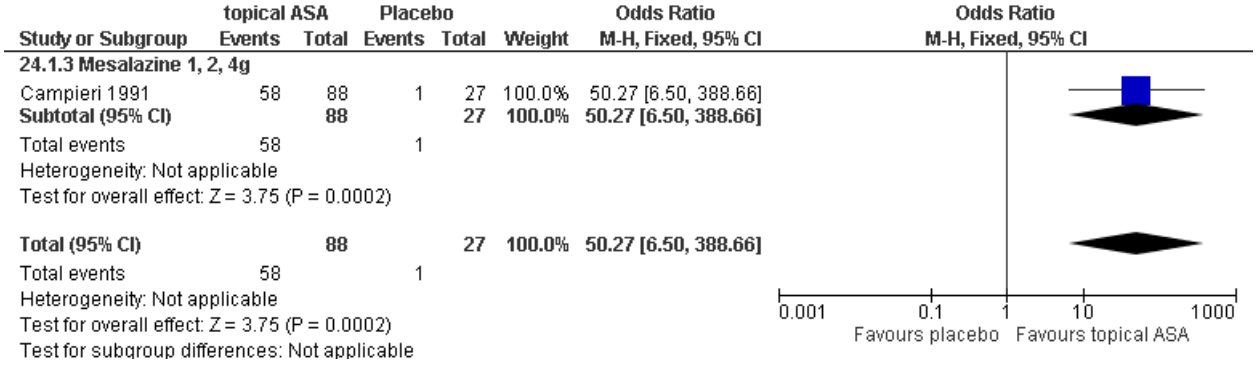


Topical ASA v placebo

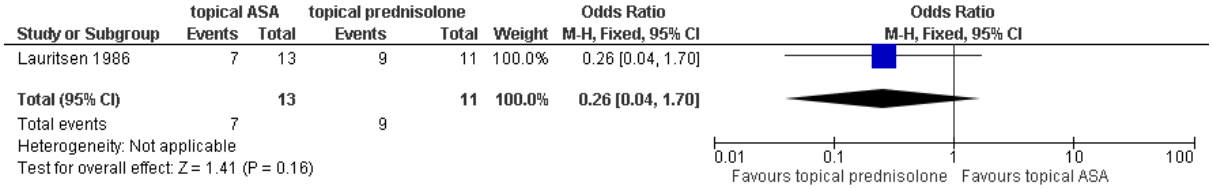


3 to 4 weeks follow-up

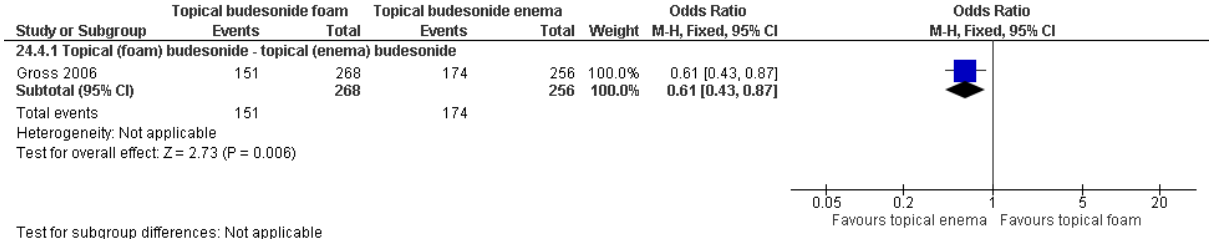
Topical ASA v placebo



Topical ASA v topical corticosteroid (prednisolone)



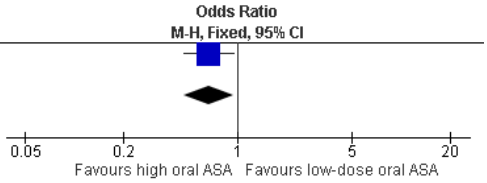
Topical corticosteroid v topical corticosteroid



Low-dose oral ASA v high-dose oral ASA

Study or Subgroup	Low-dose oral ASA Events	Total	High-dose oral ASA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sandborn 2009	65	359	91	365	100.0%	0.67 [0.47, 0.95]
Total (95% CI)		**359**		**365**	**100.0%**	**0.67 [0.47, 0.95]**
Total events	65		91			

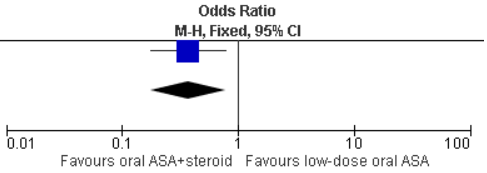
Heterogeneity: Not applicable
Test for overall effect: Z = 2.23 (P = 0.03)



Low-dose oral ASA v low-dose oral ASA and oral corticosteroid

Study or Subgroup	Low-dose oral ASA Events	Total	Low-dose ASA + steroid Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rizzello 2002	21	61	34	58	100.0%	0.37 [0.18, 0.78]
Total (95% CI)		**61**		**58**	**100.0%**	**0.37 [0.18, 0.78]**
Total events	21		34			

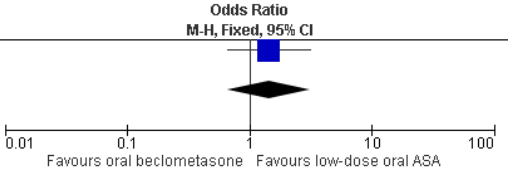
Heterogeneity: Not applicable
Test for overall effect: Z = 2.62 (P = 0.009)



Low-dose oral ASA v oral corticosteroid (beclomethasone)

Study or Subgroup	Low-dose oral ASA Events	Total	Oral beclometasone Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Campieri 2003	41	62	27	47	100.0%	1.45 [0.66, 3.16]
Total (95% CI)		**62**		**47**	**100.0%**	**1.45 [0.66, 3.16]**
Total events	41		27			

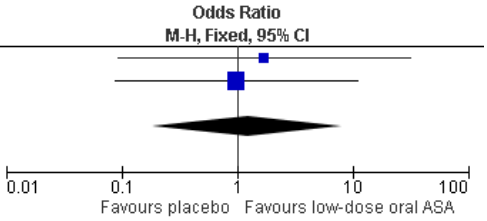
Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)



Low-dose oral ASA v placebo

Study or Subgroup	Low-dose oral ASA Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Pontes 2014	1	8	1	13	33.6%	1.71 [0.09, 31.92]
Sninsky 1991	2	106	1	52	66.4%	0.98 [0.09, 11.07]
Total (95% CI)		**114**		**65**	**100.0%**	**1.23 [0.19, 8.08]**
Total events	3		2			

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)

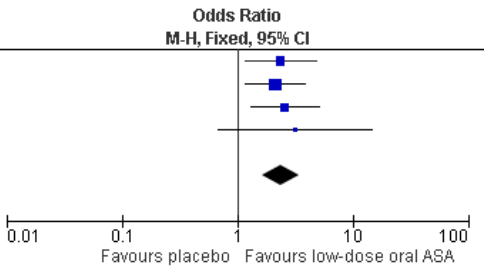


5 to 8 weeks follow-up

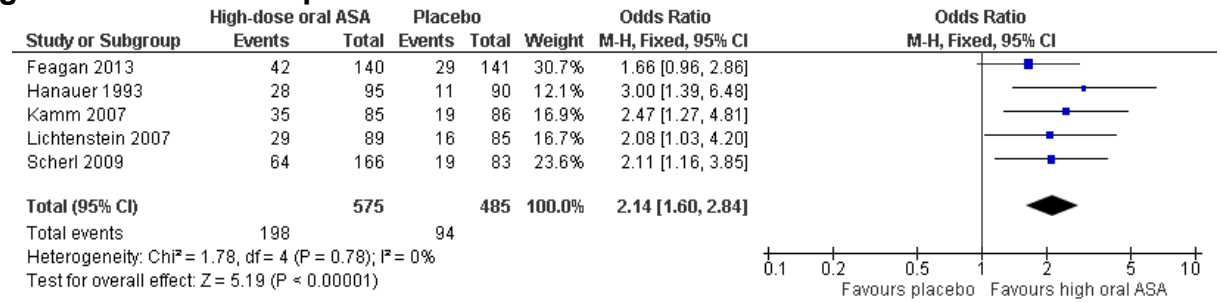
Low-dose oral ASA v placebo

Study or Subgroup	Low-dose oral ASA Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hanauer 1993	47	189	11	90	28.4%	2.38 [1.17, 4.84]
Kamm 2007	64	170	19	86	39.8%	2.13 [1.17, 3.87]
Lichtenstein 2007	33	88	16	85	25.8%	2.59 [1.29, 5.18]
Sninsky 1991	12	106	2	52	6.0%	3.19 [0.69, 14.82]
Total (95% CI)		**553**		**313**	**100.0%**	**2.38 [1.64, 3.45]**
Total events	156		48			

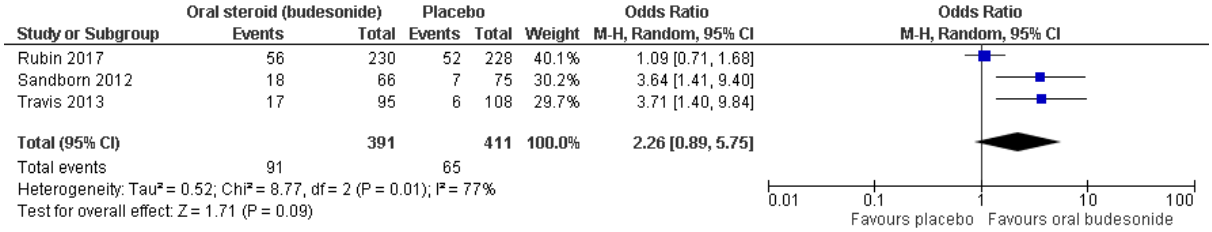
Heterogeneity: Chi² = 0.33, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.59 (P < 0.00001)



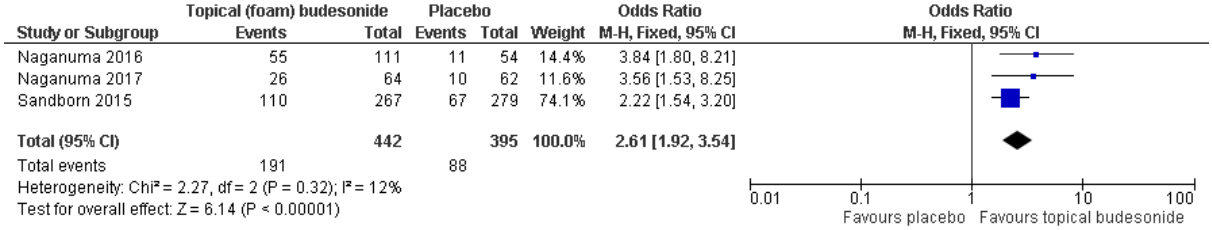
High-dose oral ASA v placebo



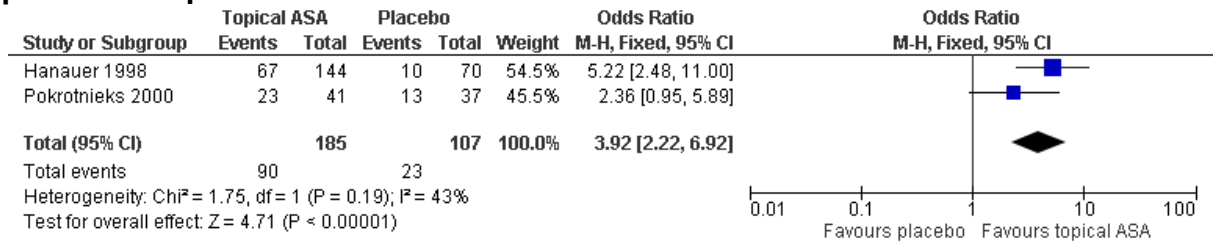
Oral corticosteroid (budesonide) v placebo



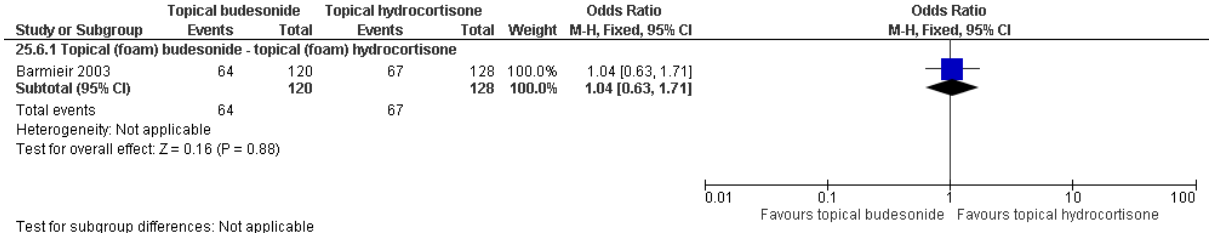
Topical corticosteroid (budesonide) v placebo



Topical ASA v placebo



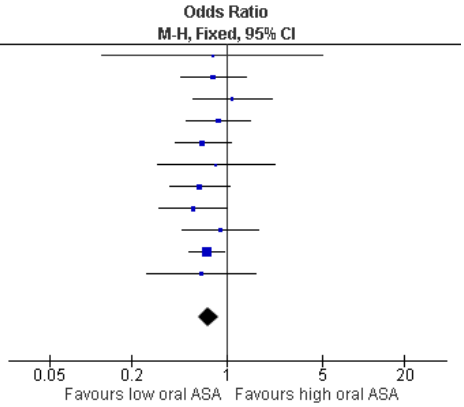
Topical corticosteroid v topical corticosteroid



Low-dose oral ASA v high-dose oral ASA

Study or Subgroup	Low-dose oral ASA Events	Total	High-dose oral ASA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dhaens 2006	4	27	2	11	0.7%	0.78 [0.12, 5.05]
Hanauer 1993	47	189	28	95	8.6%	0.79 [0.46, 1.37]
Hanauer 2005	23	77	25	89	5.0%	1.09 [0.56, 2.14]
Kamm 2007	64	170	35	85	9.0%	0.86 [0.51, 1.47]
Kruis 2003	52	103	129	213	12.8%	0.66 [0.41, 1.07]
Levine 2002	14	71	8	35	2.6%	0.83 [0.31, 2.21]
Ogata 2017	40	131	56	136	11.8%	0.63 [0.38, 1.04]
Ogata 2018	44	170	31	81	9.6%	0.56 [0.32, 0.99]
Pruitt 2002	38	77	38	73	6.1%	0.90 [0.47, 1.70]
Sandborn 2009	121	347	152	353	30.2%	0.71 [0.52, 0.96]
Suzuki 2016	10	55	14	55	3.5%	0.65 [0.26, 1.63]
Total (95% CI)		**1417**		**1226**	**100.0%**	**0.73 [0.62, 0.86]**
Total events	457		518			

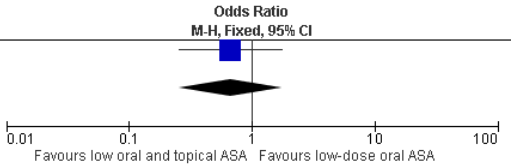
Heterogeneity: Chi² = 3.70, df = 10 (P = 0.96); I² = 0%
Test for overall effect: Z = 3.68 (P = 0.0002)



Low-dose oral ASA v low-dose oral ASA and topical ASA

Study or Subgroup	Low-dose oral ASA Events	Total	Low oral and topical ASA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Vecchi 2001	55	67	55	63	100.0%	0.67 [0.25, 1.76]
Total (95% CI)		**67**		**63**	**100.0%**	**0.67 [0.25, 1.76]**
Total events	55		55			

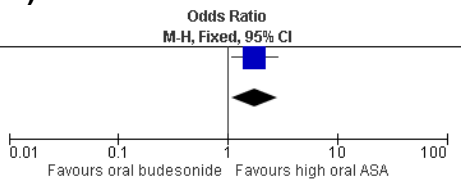
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



High-dose oral ASA v oral corticosteroid (budesonide)

Study or Subgroup	High-dose oral ASA Events	Total	Oral steroid (budesonide) Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gross 2011	72	134	56	140	100.0%	1.74 [1.08, 2.81]
Total (95% CI)		**134**		**140**	**100.0%**	**1.74 [1.08, 2.81]**
Total events	72		56			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)



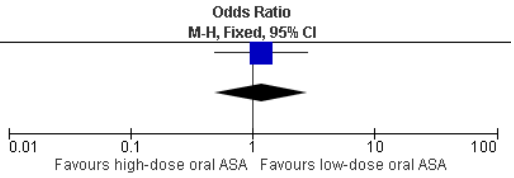
G.3 Extensive - children

6 weeks follow-up

Low-dose oral ASA v high-dose oral ASA

Study or Subgroup	Low-dose oral ASA Events	Total	High-dose oral ASA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Winter 2014	19	41	17	40	100.0%	1.17 [0.49, 2.81]
Total (95% CI)		**41**		**40**	**100.0%**	**1.17 [0.49, 2.81]**
Total events	19		17			

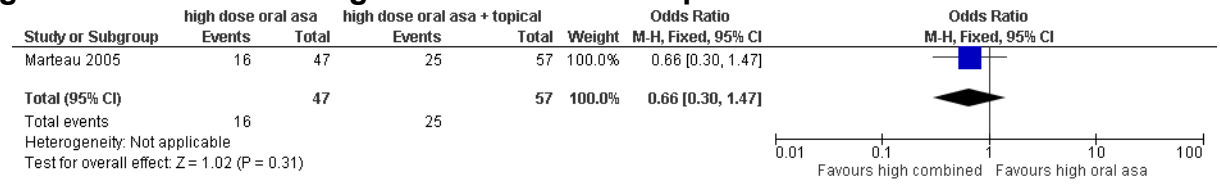
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)



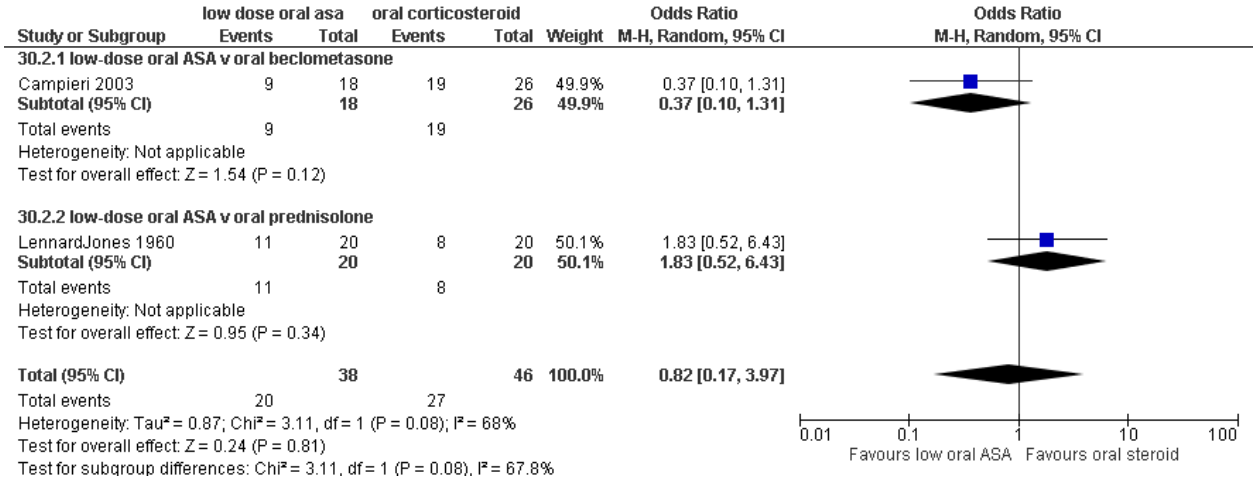
G.4 Extensive – adults

3 to 4 weeks follow-up

High-dose oral ASA vs high dose oral ASA + topical ASA

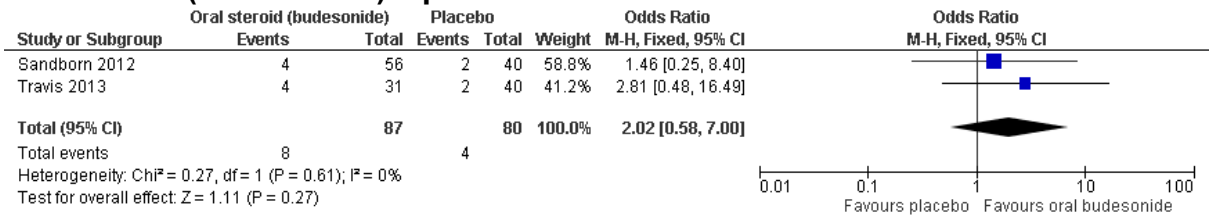


Low-dose oral ASA vs oral corticosteroid

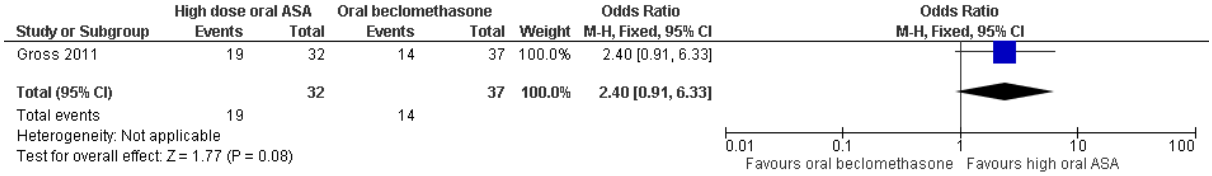


5 to 8 weeks

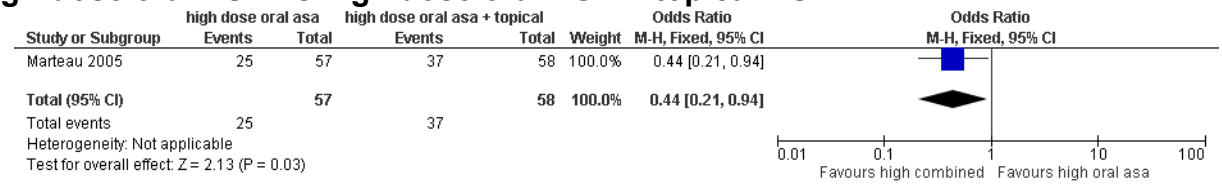
Corticosteroid (budesonide) v placebo



High-dose oral ASA v oral corticosteroid

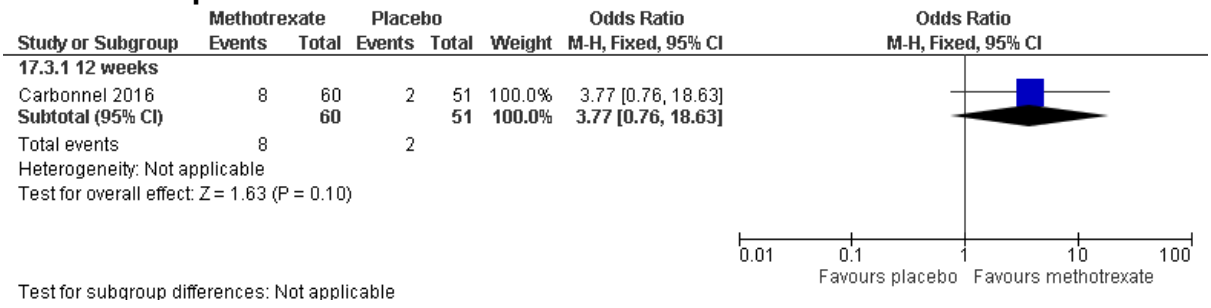


High-dose oral ASA vs high dose oral ASA + topical ASA



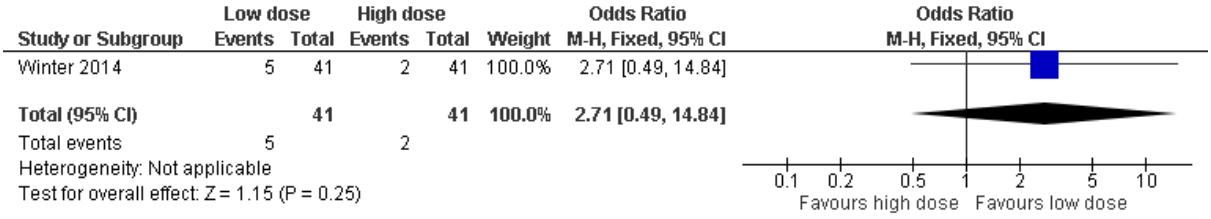
12 weeks follow-up

Methotrexate v placebo



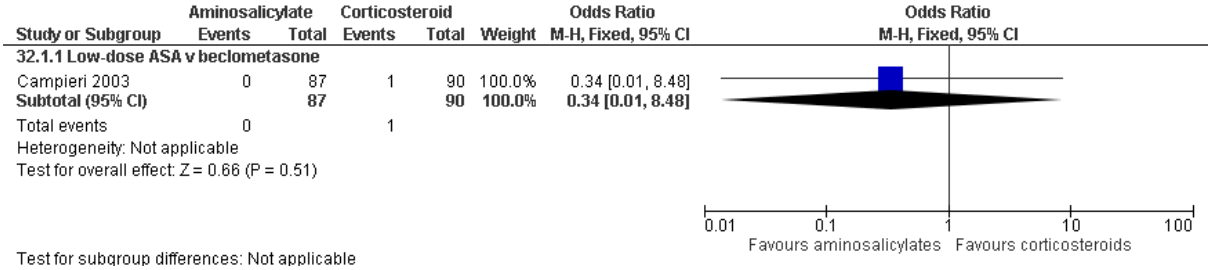
G.5 Withdrawal due to adverse events – children

Low-dose oral ASA v high-dose oral ASA



G.6 Withdrawal due to adverse events – adults

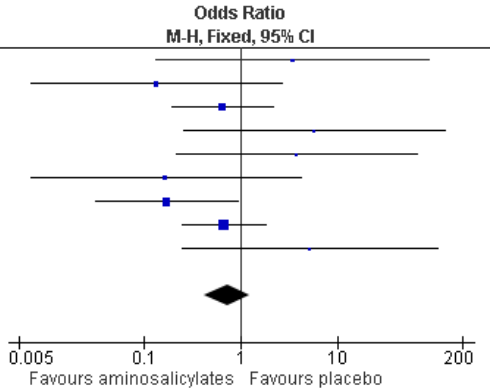
Low-dose ASA v beclomethasone



Low-dose oral ASA v Placebo

Study or Subgroup	Aminosalicylate Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dick 1964	1	21	0	23	1.5%	3.44 [0.13, 89.13]
Feurle 1989	0	53	3	52	11.6%	0.13 [0.01, 2.62]
Hanauer 1993	7	95	5	45	20.9%	0.64 [0.19, 2.13]
Hetzel 1986	2	15	0	15	1.4%	5.74 [0.25, 130.37]
Ito 2010	10	196	0	33	2.7%	3.77 [0.22, 65.92]
Kamm 2007	0	85	1	43	6.6%	0.17 [0.01, 4.15]
Lichtenstein 2007	2	89	5	42	22.1%	0.17 [0.03, 0.92]
Sandborn 2012	7	124	10	121	31.7%	0.66 [0.24, 1.81]
Sninsky 1991	2	52	0	52	1.6%	5.20 [0.24, 110.95]
Total (95% CI)		**730**		**426**	**100.0%**	**0.72 [0.42, 1.24]**
Total events	31		24			

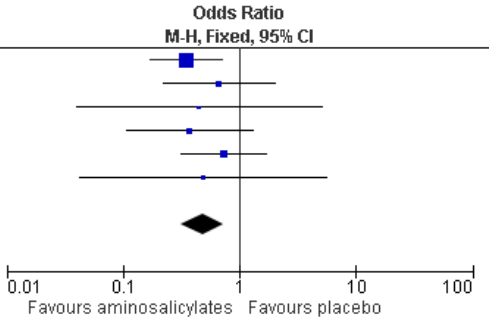
Heterogeneity: Chi² = 10.40, df = 8 (P = 0.24); I² = 23%
Test for overall effect: Z = 1.17 (P = 0.24)



High-dose oral ASA v Placebo

Study or Subgroup	Aminosalicylate Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Feagan 2013	12	140	30	141	47.1%	0.35 [0.17, 0.71]
Hanauer 1993	9	97	6	45	12.8%	0.66 [0.22, 2.00]
Kamm 2007	2	190	1	43	2.8%	0.45 [0.04, 5.04]
Lichtenstein 2007	5	88	6	43	13.1%	0.37 [0.11, 1.29]
Scherl 2009	15	166	10	83	20.9%	0.73 [0.31, 1.69]
Schroeder 1987	1	38	2	38	3.4%	0.49 [0.04, 5.60]
Total (95% CI)		**719**		**393**	**100.0%**	**0.48 [0.31, 0.74]**
Total events	44		55			

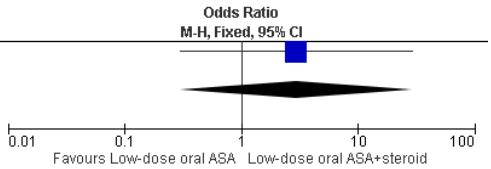
Heterogeneity: Chi² = 2.21, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.35 (P = 0.0008)



Low-dose oral ASA v low-dose oral ASA + oral beclomethasone

Study or Subgroup	Low-dose oral ASA Events	Total	Low-dose oral ASA+steroid Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rizzello 2002	3	61	1	58	100.0%	2.95 [0.30, 29.19]
Total (95% CI)		**61**		**58**	**100.0%**	**2.95 [0.30, 29.19]**
Total events	3		1			

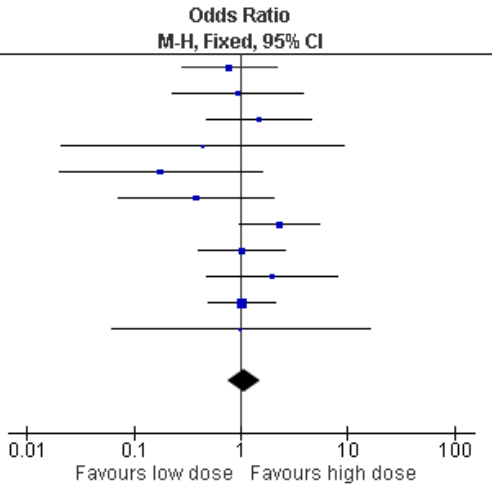
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)



Low-dose oral ASA v high-dose oral ASA

Study or Subgroup	Low dose Events	Total	High dose Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hanauer 1993	7	95	9	97	13.2%	0.78 [0.28, 2.18]
Hanauer 2005	4	139	4	129	6.4%	0.93 [0.23, 3.78]
Hanauer 2007	8	150	5	136	7.9%	1.48 [0.47, 4.63]
Kamm 2007	0	85	2	190	2.5%	0.44 [0.02, 9.28]
Levine 2002	1	53	5	51	8.0%	0.18 [0.02, 1.57]
Lichtenstein 2007	2	89	5	88	7.9%	0.38 [0.07, 2.02]
Ogata 2017	17	140	8	140	11.2%	2.28 [0.95, 5.47]
Ogata 2018	15	170	7	81	13.8%	1.02 [0.40, 2.62]
Pruitt 2002	6	89	3	84	4.6%	1.95 [0.47, 8.07]
Sandborn 2009	15	383	15	389	22.9%	1.02 [0.49, 2.11]
Suzuki 2016	1	55	1	55	1.6%	1.00 [0.06, 16.40]
Total (95% CI)		**1448**		**1440**	**100.0%**	**1.07 [0.76, 1.51]**
Total events	76		64			

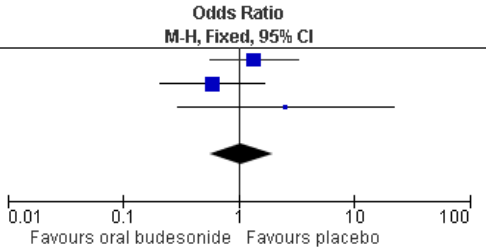
Heterogeneity: Chi² = 8.71, df = 10 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)



Oral corticosteroid (budesonide) v Placebo

Study or Subgroup	Oral budesonide Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Rubin 2017	12	255	9	255	44.4%	1.35 [0.56, 3.26]
Sandborn 2012	6	127	10	129	48.9%	0.59 [0.21, 1.67]
Travis 2013	5	253	1	128	6.7%	2.56 [0.30, 22.15]
Total (95% CI)		**635**		**512**	**100.0%**	**1.06 [0.57, 1.97]**
Total events	23		20			

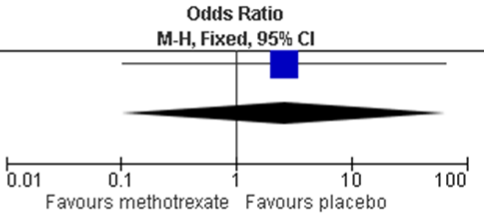
Heterogeneity: Chi² = 2.14, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 0.18 (P = 0.85)



Methotrexate (subcutaneous/IV) versus placebo

Study or Subgroup	Methotrexate Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Carbonnel 2016	1	60	0	51	100.0%	2.60 [0.10, 65.14]
Total (95% CI)		**60**		**51**	**100.0%**	**2.60 [0.10, 65.14]**
Total events	1		0			

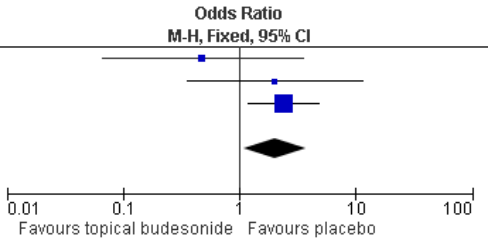
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Topical corticosteroid v Placebo

Study or Subgroup	Topical budesonide Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Naganuma 2016	2	111	2	54	17.4%	0.48 [0.07, 3.48]
Naganuma 2017	4	64	2	62	12.5%	2.00 [0.35, 11.33]
Sandborn 2015	26	268	12	278	70.1%	2.38 [1.18, 4.82]
Total (95% CI)		**443**		**394**	**100.0%**	**2.00 [1.08, 3.70]**
Total events	32		16			

Heterogeneity: Chi² = 2.23, df = 2 (P = 0.33); I² = 10%
Test for overall effect: Z = 2.22 (P = 0.03)

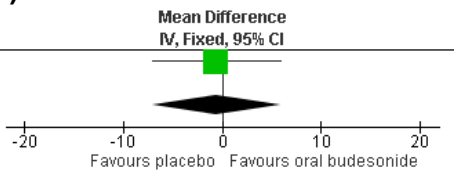


G.7 Quality of life – adults

Oral corticosteroid (Budesonide) - Placebo (IBD-QOL)

Study or Subgroup	Oral corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rubin 2017	31.1	36.07	230	31.7	34.85	228	100.0%	-0.60 [-7.10, 5.90]
Total (95% CI)			**230**			**228**	**100.0%**	**-0.60 [-7.10, 5.90]**

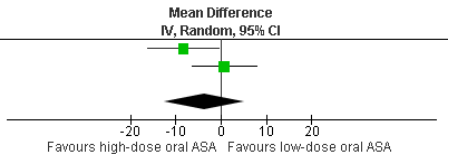
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)



Low-dose ASA v High-dose ASA (IBDQ)

Study or Subgroup	Low-dose oral aminosalicylate Mean	SD	Total	High-dose oral aminosalicylate Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Irvine 2008 ASCEND I	37.3	36.1	154	45.6	33.62	147	48.0%	-8.30 [-16.18, -0.42]
Irvine 2008 ASCEND II	38.9	37.52	195	38.2	33.13	191	52.0%	0.70 [-6.36, 7.76]
Total (95% CI)			**349**			**338**	**100.0%**	**-3.62 [-12.44, 5.19]**

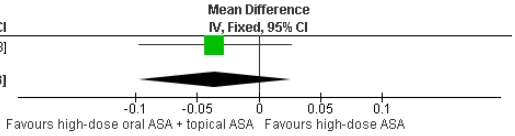
Heterogeneity: Tau² = 25.94; Chi² = 2.78, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 0.81 (P = 0.42)



High-dose ASA v high-dose oral ASA + topical ASA (EQ5D)

Study or Subgroup	High-dose oral ASA Mean	SD	Total	High-dose oral ASA + topical ASA Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Marteau 2005	0.1	0.19	56	0.136	0.16	71	100.0%	-0.04 [-0.10, 0.03]
Total (95% CI)			**56**			**71**	**100.0%**	**-0.04 [-0.10, 0.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.26)



Appendix H: GRADE tables

H.1 GRADE tables for pairwise evidence

H.1.1 Topical aminosalicylates

Topical aminosalicylates versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctitis at 2 weeks follow-up – (higher values favour topical aminosalicylates)								
2 (Campieri 1990; Campieri 1990a)	RCT	156	OR 3.47 (1.45, 8.28)	Serious[1]	No serious	No serious	No serious	Moderate
Clinical remission in adults with proctitis at 3 to 4 weeks follow-up – (higher values favour topical aminosalicylates)								
3 (Campieri 1990; Campieri 1990a; Wantabe 2013)	RCT	285	OR 7.10 (4.07, 12.40)	Serious[1]	No serious	Serious[2]	No serious	Low
Clinical remission in adults with proctitis at 5 to 8 weeks follow-up – (higher values favour topical aminosalicylates)								
1 (Pokrotnieks 2000)	RCT	33	OR 1.75 (0.43, 7.17)	No serious	No serious	N/A[3]	Very serious[4]	Low
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 2 weeks follow-up – (higher values favour topical aminosalicylates)								
1 (Campieri 1991)	RCT	111	OR 13.71 (1.77, 106.21)	No serious	No serious	N/A[3]	No serious	High
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (higher values favour topical aminosalicylates)								
1 (Campieri 1991)	RCT	115	OR 50.27 (6.50, 388.66)	No serious	No serious	N/A[3]	No serious	High
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour topical aminosalicylates)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2 (Hanauer 1998; Pokrotneiks 2000)	RCT	292	OR 3.92 (2.22, 6.92)	No serious	No serious	Serious[2]	No serious	Moderate

1 Greater than 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.
2 I^2 value was greater than 33.3% and less than 66.7%.
3 Inconsistency not applicable as effect size is from a single study
4 95% confidence intervals crossed two MIDs

Topical aminosalicylates versus topical corticosteroid

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (lower values favour topical prednisolone)								
1 (Lauritsen 1986)	RCT	24	OR 0.26 (0.04, 1.70)	Serious[1]	No serious	N/A[2]	Very serious[3]	Very low

1 Moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study
3 95% confidence intervals crossed two MIDs

H.1.2 Topical immunomodulator

Topical immunomodulator (ointment) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctitis at 5 to 8 weeks follow-up – (higher values favour tacrolimus ointment)								
1 (Lawrance 2017)	RCT	21	OR 17.77 (0.84, 377.40)	No serious	Serious[1]	N/A	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1 Indirect treatment preparation as ointment form of tacrolimus not used for proctitis in clinical practice.
2 95% confidence intervals crossed one MID.

H.1.3 Topical corticosteroids

Topical corticosteroid v placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 2 weeks follow-up – (higher values favour topical prednisolone)								
1 (Binder 1987)	RCT	117	OR 0.49 (0.23, 1.03)	Serious[1]	No serious	N/A[2]	Serious[3]	Low
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour topical budesonide)								
3 (Naganuma 2016; Naganuma 2017; Sandborn 2015)	RCT	837	OR 2.61 (1.92, 3.54)	Serious[4]	No serious	No serious	No serious	High
Withdrawal due to adverse events (all extents of disease) up to 10 weeks follow-up - (lower values favour topical budesonide)								
3 (Naganuma 2016; Naganuma 2017; Sandborn 2015)	RCT	837	OR 2.00 (1.08, 3.70)	Serious[4]	No serious	No serious	Serious[3]	Low

1 Moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study
3 95% confidence intervals crossed one MID.
4 Greater than 33.3% of the weight in a meta-analysis came from studies at moderate risk of bias.

Topical budesonide (foam) v topical budesonide (enema)

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (higher values favour foam budesonide)								
1 (Gross 2006)	RCT	524	OR 0.61 (0.43, 0.87)	Serious[1]	No serious	N/A[2]	Serious[3]	Low

1 Moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study
3 95% confidence intervals crossed one MID

Topical budesonide (foam) v topical hydrocortisone (foam)

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour foam budesonide)								
1 (Bar-Mieir 2003)	RCT	248	OR 1.04 (0.63, 1.71)	Very serious[1]	No serious	N/A[2]	Very serious[3]	Very low

1 High risk of bias (open-label trial).
2 Inconsistency not applicable as effect size is from a single study
3 95% confidence intervals crossed two MIDs.

H.1.4 Standard-dose oral aminosalicylates

No of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctitis at 5 to 8 weeks follow-up – (higher values favour low-dose oral aminosalicylates)								
1 (Ito 2010)	RCT	225	OR 5.14 (1.51, 17.50)	Serious[1]	No serious	N/A[2]	No serious	Moderate
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (higher values favour low-dose oral aminosalicylates)								
2 (Pontes 2014; Sninsky 1991)	RCT	179	OR 1.23 (0.19, 8.08)	No serious	No serious	No serious	Very serious[3]	Low

No of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour low-dose oral aminosalicylates)								
4 (Hanauer 1993; Kamm 2007; Lichtenstein 2007; Sninsky 1991)	RCT	866	OR 2.38 (1.64, 3.45)	No serious	No serious	No serious	No serious	High
Withdrawal due to adverse events (all extents of disease) up to 10 weeks follow-up - (lower values favour low-dose oral aminosalicylates)								
9 (Dick 1964; Feurle 1989; Hanauer 1993; Hetzel 1986; Ito 2010; Kamm 2007; Lichtenstein 2007; Sandborn 2012; Sninsky 1991)	RCT	1156	OR 0.72 (0.42, 1.24)	Serious[4]	No serious	No serious	Serious[5]	Low

1 Moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study.
3 95% confidence intervals crossed two MIDs.
4 Greater than 33% of the studies were at moderate risk of bias.
5 95% confidence intervals crossed one MID.

Standard-dose oral aminosalicylates versus topical aminosalicylates

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctitis at 2 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								
1 (Gionchetti 1998)	RCT	58	OR 0.16 (0.05, 0.51)	Serious[1]	No serious	N/A[2]	No serious	Moderate
Clinical remission in adults with proctitis at 3 to 4 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								
1 (Gionchetti 1998)	RCT	58	OR 0.08 (0.02, 0.33)	Serious[1]	No serious	N/A[2]	No serious	Moderate

1 Moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study.

Standard-dose oral aminosalicylates versus combined standard-dose oral aminosalicylates and topical aminosalicylates

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								
1 (Vecchi 2001)	RCT	130	OR 0.67 (0.25, 1.76)	No serious	No serious	N/A[1]	Very serious[2]	Low

1 Inconsistency not applicable as effect size is from a single study.
2 95% confidence intervals crossed two MIDs.

Standard-dose oral aminosalicylates versus high-dose oral aminosalicylates

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								
1 (Sandborn 2009)	RCT	724	OR 0.67 (0.47, 0.95)	No serious	No serious	N/A[1]	Serious[2]	Moderate
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								
10 (Dhaens 2006; Hanauer 1993; Hanauer 2005; Kamm 2007; Kruis 2003; Levine 2002; Ogata 2017; Ogata 2018; Pruitt 2002; Sandborn 2009; Suzuki 2016)	RCT	2643	OR 0.73 (0.62, 0.86)	No serious	No serious	No serious	Serious[2]	Moderate
Clinical remission in children with extensive ulcerative colitis 6 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Winter 2014)	RCT	81	OR 1.17 (0.49, 2.81)	Serious[3]	No serious	N/A[1]	Very serious[4]	Very low
Withdrawal due to adverse events (all extents of disease) up to 10 weeks follow-up - (lower values favour standard-dose oral aminosalicylates)								
11 (Hanauer 1993; Hanauer 2005; Hanauer 2007; Kamm 2007; Levine 2002; Lichtenstein 2007; Ogata 2017; Ogata 2018; Pruitt 2002; Sandborn 2009; Suzuki 2016)	RCT	2	OR 1.07 (0.76, 1.51)	No serious	No serious	No serious	Very serious[4]	Low
Withdrawal due to adverse events in children with extensive ulcerative colitis at 6 weeks follow-up - (lower values favour standard-dose oral aminosalicylates)								
1 (Winter 2014)	RCT	82	OR 2.71 (0.49, 14.84)	Serious[3]	No serious	N/A[1]	Very serious[4]	Very low
Quality of life using inflammatory bowel disease questionnaire (IBDQ) in adults (extent of disease not reported) - change from baseline to 6 weeks follow-up – (higher values favour standard-dose oral aminosalicylates)								
2 (Irvine 2008 ASCEND I; Irvine 2008 ASCEND II)	RCT	687	MD -3.62 (-12.44, 5.19)	No serious	No serious	N/A[1]	Very serious[4]	Low

1 Inconsistency not applicable as effect size is from a single study.
2 95% confidence intervals crossed one MID.
3 Moderate risk of bias.
4 95% confidence intervals crossed two MIDs.

Standard- dose oral aminosalicylates versus oral corticosteroid

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (lower values favour beclometasone)								
1 (Campieri 2003)	RCT	109	OR 1.45 (0.66, 3.16)	Very serious[1]	No serious	N/A[2]	Very serious[3]	Very low
Clinical remission in adults with extensive ulcerative colitis at 3 to 4 weeks follow-up – (lower values favour beclometasone)								
1 (Campieri 2003)	RCT	44	OR 0.37 (0.10, 1.31)	Very serious[1]	No serious	N/A[2]	Very serious[3]	Very low
Clinical remission in adults with extensive ulcerative colitis at 3 to 4 weeks follow-up – (lower values favour prednisolone)								
1 (Lennard-Jones 1960)	RCT	40	OR 1.83 (0.52, 6.43)	No serious	No serious	N/A[2]	Very serious[3]	Low
Withdrawal due to adverse events (all extents of disease) up to 10 weeks follow-up - (higher values favour beclometasone)								
1 (Campieri 2003)	RCT	177	OR 0.34 (0.01, 8.48)	Serious[4]	No serious	N/A[2]	Very serious[3]	Very low

1 High risk of bias for clinical remission.
2 Inconsistency not applicable as effect size is from a single study.
3 95% confidence intervals crossed two MIDs.
4 Moderate risk of bias for withdrawal due to adverse events.

Standard-dose oral aminosalicylates versus combined standard-dose oral aminosalicylates and oral corticosteroid

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 3 to 4 weeks follow-up – (lower values favour oral mesalazine combined with oral beclometasone)								
1 (Rizzello 2002)	RCT	119	OR 0.37 (0.18, 0.78)	Serious[1]	No serious	N/A[2]	No serious	Moderate
Withdrawal due to AE (all extents of disease) up to 10 weeks follow-up – (lower values favour oral mesalazine combined with oral beclometasone)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Rizzello 2002)	RCT	119	OR 2.95 (0.30, 29.19)	Serious[1]	No serious	N/A[2]	Very serious[3]	Very low

1 Moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study.
3 95% confidence intervals crossed two MIDs.

H.1.5 High-dose oral aminosalicylates

High-dose oral aminosalicylates versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour high-dose oral aminosalicylates)								
5 (Feagan 2013; Hanauer 1993; Kamm 2007; Lichtenstein 2007; Scherl 2009)	RCT	1060	OR 2.14 (1.60, 2.84)	Serious[1]	No serious	No serious	No serious	Moderate
Withdrawal due to AE (all extents of disease) up to 10 weeks follow-up – (lower values favour high-dose oral aminosalicylates)								
6 (Feagan 2013; Hanauer 1993; Kamm 2007; Lichtenstein 2007; Scherl 2009; Schroeder 1987)	RCT	1112	OR 0.48 (0.31, 0.74)	Serious[1]	No serious	No serious	No serious	Moderate

1 Greater than 33% of the studies were at moderate risk of bias.

High-dose oral aminosalicylates versus oral corticosteroid (budesonide)

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour high-dose oral aminosalicylates)								
1 (Gross 2011)	RCT	274	OR 1.74 (1.08, 2.81)	Serious[1]	No serious	N/A[2]	Serious[3]	Low
Clinical remission in adults with extensive ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour high-dose oral aminosalicylates)								
1 (Gross 2011)	RCT	69	OR 2.40 (0.91, 6.33)	Serious[1]	No serious	N/A[2]	Serious[3]	Low

1 Study at moderate risk of bias.
2 Inconsistency not applicable as effect size is from a single study.
3 95% confidence intervals crossed one MID.

High-dose oral aminosalicylates versus combined high-dose oral aminosalicylates and topical aminosalicylates

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with extensive ulcerative colitis at 3 to 4 weeks follow-up – (higher values favour high-dose oral aminosalicylates)								
1 (Marteau 2005)	RCT	104	OR 0.66 (0.30, 1.47)	No serious	No serious	N/A[1]	Very serious[2]	Low
Clinical remission in adults with extensive ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour high-dose oral aminosalicylates)								
1 (Marteau 2005)	RCT	115	OR 0.44 (0.21, 0.94)	No serious	No serious	N/A[1]	Serious[3]	Moderate
Quality of life (EQ-5D) in adults with extensive ulcerative colitis - change from baseline to 8 weeks follow-up – (higher values favour high -dose oral aminosalicylates)								
1 (Marteau 2005	RCT	127	MD -0.04 (-0.10, 0.03)	No serious	No serious	N/A[1]	No serious	High

1 Inconsistency not applicable as effect size is from a single study.
2 95% confidence intervals crossed two MIDs.
3 95% confidence intervals crossed one MID.

H.1.6 Oral corticosteroids

Oral corticosteroids versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with proctosigmoiditis and left-sided ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour budesonide)								
3 (Rubin 2017; Sandborn 2012; Travis 2013)	RCT	802	OR 2.26 (0.89, 5.75)	Serious[1]	No serious	Very serious[2]	Serious[3]	Very low
Clinical remission in adults with extensive ulcerative colitis at 5 to 8 weeks follow-up – (higher values favour budesonide)								
2 (Sandborn 2012; Travis 2013)	RCT	167	OR 2.02 (0.58, 7.00)	Serious[1]	No serious	No serious	Very serious[4]	Very low
Withdrawal due to adverse events (all extents of disease) up to 10 weeks follow-up – (lower values favour budesonide)								
3 (Rubin 2017; Sandborn 2012; Travis 2013)	RCT	1147	OR 1.06 (0.57, 1.97)	Serious[1]	No serious	No serious	Very serious[4]	Very low
Quality of life using Inflammatory Bowel Disease Quality of Life Questionnaire (IBD-QoL) in adults with all extents of ulcerative colitis - change from baseline to 8 weeks follow-up – (higher values favour budesonide)								
1 (Rubin 2017)	RCT	458	MD -0.60 (-7.10, 5.90)	Serious[5]	No serious	N/A[6]	Very serious[4]	Very low

1 Greater than 33% of the studies were at moderate risk of bias.
2 I2 value greater than 66.7%.
3 95% confidence intervals crossed one MID.
4 95% confidence intervals crossed two MIDs.
5 Moderate risk of bias
6 Inconsistency not applicable as effect size is from a single study.

H.1.7 Methotrexate versus placebo

Methotrexate versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Clinical remission in adults with adults with extensive ulcerative colitis at 12 weeks follow-up – (higher values favour methotrexate)								
1 (Carbonnel 2016)	RCT	111	OR 3.40 (0.76, 15.30)	No serious	No serious	N/A	Very serious[1]	Low
Withdrawal due to adverse events with extensive ulcerative colitis at 12 weeks follow-up – (lower values favour methotrexate)								
1 (Carbonnel 2016)	RCT	111	OR (2.60 (0.10, 65.14)	No serious	Serious[2]	N/A	Very serious[1]	Very low

1. 95% confidence intervals crossed two MIDs.
2. Indirect treatment: only subcutaneous considered in evidence review.

H.2 GRADE tables for indirect evidence from network meta-analysis

Proctitis

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
Clinical remission in adults: 0 to 2 weeks								
3	RCT	Serious[1]	No serious	No serious	No serious	214	See Appendix I	Moderate
Clinical remission in adults: 0 to 4 weeks								
4	RCT	Serious[1]	No serious	No serious	No serious	343	See Appendix I	Moderate
Clinical remission in adults: 5 to 8 weeks								
3	RCT	No serious	Serious[2]	No serious	Serious[3]	279	See Appendix I	Low
1 Greater than 33% of the studies were at moderate risk of bias.								

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
2 DIC statistic is lower in random effects model. *3 Analysis could not differentiate any clinically meaningful differences.*								

Proctosigmoiditis and left-sided

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
Clinical remission in adults: 0 to 2 weeks								
2	RCT	Serious[1]	No serious	No serious	No serious	201	See Appendix I	Moderate
Clinical remission in adults: 0 to 4 weeks								
8	RCT	No serious	No serious	No serious	No serious	1356	See Appendix I	High
Clinical remission in adults: 5 to 8 weeks								
26	RCT	Serious[1]	Serious[2]	No serious	No serious	6352	See Appendix I	Low
1 Greater than 33% of the studies were at moderate risk of bias. *2 DIC statistic is lower in random effects model.*								

Extensive

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
Clinical remission in adults: 0 to 4 weeks								
3	RCT	Serious[1]	No serious	Serious[2]	No serious	188	See Appendix I	Low
Clinical remission in adults: 5 to 8 weeks								
4	RCT	Serious[1]	No serious	No serious	No serious	331	See Appendix I	Moderate

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
1 Greater than 33% of the studies were at high risk of bias. *2 Serious indirectness as the network meta-analysis was connected by using evidence (high-dose oral aminosalicylates versus standard dose oral aminosalicylates) from proctosigmoiditis and left-sided disease.*								

All extents of disease

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	No of participants	Effect size (95% CI)	Quality
Withdrawal due to adverse events								
28	RCT	Very serious[1]	No serious	No serious	No serious	6594	See Appendix I	Very low
1 Greater than 33% of the studies were at moderate risk of bias.								

Appendix I: Network meta-analysis

I.1 General methods

For details of the generic methods adopted for these analyses, please see Appendix B:

I.1.1 Analyses undertaken

For the critical effectiveness outcome of clinical remission, the models were fitted for 3 different extents of disease:

- Proctitis
- Proctosigmoiditis and left-sided
- Extensive

at up to 3 different timepoints (depending on availability of data):

- 2 weeks
- 0–4 weeks
- 5–8 weeks

I.1.2 Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

Results were reported summarising 10,000 samples from the posterior distribution of each model, thinned from 100,000 iterations, having first run and discarded 10,000 ‘burn-in’ iterations. Three separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal (0,10000) priors, and the between-trial standard deviations used in random-effects models were given Uniform(0,5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed- and random-effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed-effect model was considered to provide an equivalent fit to the data in a more parsimonious analysis, and was preferred. The goodness-of-fit of each model was assessed using the total residual deviance. This value was compared tothe total number of data points to check if the model fit can be improved. A value closer to the number of data points was preferred.

Model selection was based on the most evidence available at a time point of analysis and this was undertaken in proctosigmoiditis and left-sided at 5 to 8 weeks.

For clinical remission, a binomial likelihood and logit link model was fitted for different extents of disease at different clinically important follow-up time points. Using a logit model implies one of the following assumptions: that all people with ulcerative colitis who reach the end-point do so by some specific follow-up time, and further follow-up would make no difference;

or that the proportional odds assumption holds. In one network, clinical remission in extensive disease at up to 4 weeks follow-up, the network could not be connected with the evidence available. However, options to connect the network to provide the committee with results were examined. No data was available from extensive disease at a different time-point. The network could be connected by using the relative effectiveness of standard-dose oral aminosalicylate compared to high-dose oral aminosalicylate from proctosigmoiditis and left-sided extent of disease. The committee agreed that this was a reasonable solution as at at the level of relative effects, they believed a similar difference could be expected between low- and high-dose oral aminosalicylates. Further details can be found in I.3.1.7.

For withdrawal due to adverse events, there was limited evidence available at each clinically important follow-up time, as the majority of studies reported withdrawals at final follow-up. To incorporate all available evidence and comparisons, a binomial likelihood and cloglog link model was fitted for all extents of disease. To account for the different length of follow-up in each trial (data from up to 10 weeks was available), an underlying Poisson process for each trial arm is assumed, with a constant event rate. The assumptions made in this model are, namely, that the hazards are constant over the entire duration of follow-up. This implies homogeneity of the hazard across people with ulcerative colitis in each trial.

I.2 Model selection

I.2.1 Potential models

The main challenge presented by the dataset of included evidence was to identify the most appropriate way of defining the interventions. The data could be subdivided in a variety of different ways to form more or less granular networks of comparisons – i.e. interventions could be ‘lumped’ or ‘split’, according to multiple characteristics. The critical factors were dose, mode of administration, preparation, agent and class – e.g. a 500 mg suppository of Asacol, which is a preparation of mesalazine, which is an aminosalicylate. The committee advised that all these factors could potentially have an influence on probability of remission. However, in order to construct a tractable decision problem, it was agreed that dose could be dichotomised into ‘low’ and ‘high’ categories and that, once this had been done, there was little reason to distinguish between different preparations of the same agent (while, for example, different preparations of mesalazine are known to have different potency, there is broad agreement as to equivalent dosages, so that a ‘low’ or ‘high’ dose of each agent would be expected to have similar effects).

The remaining characteristics were combined to define 8 models that – provided appropriate data were available – could reasonably be fitted:

- 01. class level
  - e.g. aminosalicylates versus corticosteroids versus placebo
  - all agents, doses and modes of delivery combined
- 02. drug level
  - e.g. mesalazine versus balsalazide versus budesonide
  - all doses and modes of delivery combined
- 03. dose and class
  - e.g. low-dose aminosalicylates versus high-dose aminosalicylates versus corticosteroids
  - all agents and modes of delivery combined
- 04. dose and drug
  - e.g. low-dose mesalazine versus high-dose mesalazine versus high-dose balsalazide versus low-dose budesonide

- all modes of delivery combined
- 05. mode of delivery and class
  - e.g. oral aminosalicylates versus topical aminosalicylates versus oral corticosteroids versus topical corticosteroids
  - all doses and agents combined
- 06. mode of delivery and drug
  - e.g. oral mesalazine versus topical mesalazine versus oral balsalazide versus oral budesonide versus topical budesonide
  - all doses combined
- 07. mode of delivery and dose and class
  - e.g. low-dose oral aminosalicylates versus high-dose oral aminosalicylates versus low-dose topical aminosalicylates versus low-dose oral corticosteroids versus high-dose topical corticosteroids
  - all agents combined
- 08. mode of delivery and dose and drug
  - e.g. low-dose oral mesalazine versus high-dose oral mesalazine versus low-dose topical mesalazine versus low-dose oral balsalazide versus low-dose oral budesonide versus low-dose topical budesonide

In addition, an expanded mode of delivery model was tested, which expands topical treatments to different topical preparations, including: liquid enema, foam, suppository or ointment. The expanded mode was named mode2 and the following were tested:

- 09. mode2 and class
  - e.g. oral aminosalicylates versus topical (enema) aminosalicylates versus topical (foam) aminosalicylates versus oral corticosteroids versus topical (enema) corticosteroids versus topical (foam) corticosteroids
  - all doses and agents combined
- 10. mode2 and drug
  - e.g. oral mesalazine versus oral balsalazide versus topical (enema) mesalazine versus topical (foam) mesalazine versus oral budesonide versus topical (enema) budesonide versus topical (foam) budesonide
  - all doses combined
- 11. mode2 and dose and class
  - e.g. low-dose oral aminosalicylates versus high-dose oral aminosalicylates versus low-dose topical (enema) aminosalicylates versus low-dose topical (foam) aminosalicylates versus low-dose oral corticosteroids versus high-dose oral corticosteroids versus low-dose topical (enema) corticosteroids versus low-dose topical (foam) corticosteroids
  - all agents combined
- 12. mode2 and dose and drug
  - e.g. low-dose oral mesalazine versus high-dose oral mesalazine versus low-dose oral balsalazide versus low-dose topical (enema) mesalazine versus low-dose topical (foam) mesalazine versus low-dose oral budesonide versus high-dose oral budesonide versus low-dose topical (enema) budesonide versus low-dose topical (foam) budesonide

In practice, it was not possible to make all these distinctions in all cases. For all classes of treatment other than oral aminosalicylates, there was no meaningful heterogeneity in dosage – that is, all studied drugs could be considered ‘low dose’ (also referred to as ‘standard dose’) – so the distinction was only applied to oral aminosalicylates (at class and drug level). Data constraints meant it was also not possible to explore the appropriateness of analysing oral corticosteroids as a class or at agent level as, while multiple different agents appear at

least once in the overall evidence base, individual networks only contained a single option within the class. Therefore, oral corticosteroids were analysed at drug level in all models as were topical corticosteroids for consistency.

Consideration was given to whether more parsimonious models could be constructed using a meta-regression approach to quantify the shared effect of characteristics across different drugs – e.g. a shared covariate for topical administration that could apply equally to different agents and classes, or a shared effect of dosage that could be assumed to apply across the dataset. However, the committee advised that it would be hard to support such assumptions as, at least at the class level, different mechanisms of action would be expected to interact differently with these overarching factors.

Consideration was also given to the use of class-level models that allowed an exchangeable effect of agents-within-class. While, in theory, this would have been an attractive approach, in practice, data were much too sparse to be able to identify a class-level heterogeneity parameter, and constraining this parameter with a strongly informative prior was considered no more helpful than testing models assuming independent and identical effects.

I.2.2 Choosing the best model

If plentiful data had been available for each extent of disease and timepoint, it would theoretically have been possible to assess goodness of fit for the different models in every case. In practice, paucity of data made such an approach impossible. Moreover, it would not have been desirable to present different models for different datasets, as it would be difficult to derive coherent recommendations and especially challenging to configure the health economic model to vary its unit of analysis between different extents and/or timepoints. It would also have demanded that up over 200 models would have to be fitted, which was considered impractical.

Therefore, thorough model selection was undertaken on the largest dataset available (proctosigmoiditis and left-sided disease at 5–8 weeks), and the model identified as optimal was used in all other datasets (although fixed- or random-effects models were fitted and the better choice selected for each network – see Appendix B: for general principles for preferring fixed- or random-effects approaches).

Goodness-of-fit measures for the candidate models are presented in Table 11. The following observations can be made:

- In simpler models that do not account for mode of delivery and/or dose (01–06, 09–10), the total residual deviance of fixed-effect models is always conspicuously higher than the number of datapoints in the model. Introducing a random-effects term to these models produces results in lower deviance, and the Deviance Information Crierion (DIC) is always superior compared with the analogous fixed-effect model. Once mode of delivery and dose are accounted for (models 07–08, 11–12), fixed-effect models provide a much more acceptable fit to the data, and it is noticeable that the random-effects distribution required to account for any residual heterogeneity becomes much narrower. Therefore, we should only consider models that make these distinctions.
- There is no evidence that distinguishing between aminosalicylates is desirable. Comparing the random-effects terms for pairs of models (e.g. 05 -v- 06 & 07 -v- 08) shows that no additional heterogeneity is explained in the drug-level analysis. The DIC is somewhat higher for the models that distinguish between drugs, suggesting that the inclusion of this additional information provides no benefit – indeed, it may introduce the risk of overfitting. We also note that, in the most granular analysis available (model 12), there is no evidence of different effect between the 2 aminosalicylates for which evidence is available (mesalazine and balsalazide); indeed, at low dose, the NMA estimates an odds ratio of 1.01 (0.33, 2.75) between the 2 (see cells highlighted in yellow in Table 12).

For all these reasons, we concluded that it would not be helpful to distinguish between aminosalicylates at the level of individual agents.

- It is more difficult to discern whether the introduction of an expanded classification of mode of administration (i.e. 'mode2' as opposed to 'mode') results in a better model. Goodness of fit is very similar between models 07 and 11 (which are the 2 remaining models we would be interested in, given the decisions outlined above). The estimated odds ratio for enema -v- foam in Table 12 is 2.27 (0.69, 7.61), and we found similar uncertainty in exploratory analyses in other extents of disease – e.g. for proctitis (where topical treatments are more universally used) at 3–4 weeks, aminosalicylate suppositories were associated with an odds ratio of 0.93 (0.19, 4.86) compared with liquid enemas. Given the substantial uncertainty around this point, we concluded that we should not attempt to distinguish between different modes of topical administration, as it was clear that no useful results would be possible.

Taking all the above into account, we determined that the optimal model was 07 – that is, treating aminosalicylates as a class (but distinguishing between low- and high-dose oral regimens), and making a distinction between oral and topical modes of administration (but not different types of topical preparation). Having adopted this model, it was clear that the fixed-effect analysis provided a good fit to the data, so there was no need to introduce the additional random-effects term. However, as noted above, this decision was repeated for each analysis in turn when the model was fitted. In practice, fixed-effect models were preferred in every case, either because they demonstrably provided no worse fit to the data than the analogous random-effects analysis or because there were insufficient data to estimate a heterogeneity parameter. The comparison of fixed-effect and random-effect analysis is presented in Table 13.

A similar approach was used for selecting the most appropriate model for withdrawal due to adverse events. No differences were found in topical foam or topical liquid aminosalicylates or drugs. Therefore, a model incorporating mode, dose and class model was fitted. The WinBUGS code used in the model selection process for estimating relative treatment effects is provided below in section I.4. Baseline synthesis models to inform the cost-effectiveness analysis are discussed in Appendix M.

Table 11: Model selection for network meta-analysis

Outcome	Number of studies	Participants	Datapoints	Model	Number of unique options	FE/RE	Total residual deviance	DIC	Standard deviation of random effects distribution (95%CI)
Clinical remission: 5–8 weeks	23	5,863	57	01. Class	4	FE	77.46	360.8	n/a
						RE	56.95	352.3	0.28 (0.11, 0.47)
				02. Drug	5	FE	78.39	362.6	n/a
						RE	57.01	353.6	0.29 (0.12, 0.49)
				03. Dose_class	5	FE	69.51	353.7	n/a
						RE	59.29	352.1	0.20 (0.01, 0.42)
				04. Dose_drug	7	FE	70.69	357.0	n/a
						RE	59.11	354.3	0.23 (0.04, 0.44)
				05. Mode_class	7	FE	68.05	354.3	n/a
						RE	57.02	351.7	0.21 (0.04, 0.42)
				06. Mode_drug	8	FE	68.82	356.1	n/a
						RE	57.78	353.6	0.22 (0.04, 0.43)
				07. Mode_dose_class	8	FE	58.18	345.4	n/a
						RE	55.91	346.7	0.10 (0.00, 0.31)
				08. Mode_dose_drug	10	FE	59.89	349.1	n/a
						RE	57.00	350.6	0.13 (0.01, 0.35)
				09. Mode2_class	8	FE	67.35	354.7	n/a
						RE	57.39	352.7	0.20 (0.02, 0.41)
				10. Mode2_drug	9	FE	68.20	356.6	n/a
						RE	57.25	353.6	0.22 (0.03, 0.43)
				11. Mode2_dose_class	9	FE	57.49	345.8	n/a
						RE	55.82	347.6	0.09 (0.00, 0.31)
				12. Mode2_dose_drug	11	FE	59.15	349.4	n/a
						RE	57.09	351.1	0.11 (0.00, 0.33)

Table 12: Clinical remission for proctosigmoiditis and left-sided at 5–8 weeks' follow-up: expanded mode, dose and drug model (FE).

	low-dose mesalazine - oral	budesonide - oral	budesonide - topical (foam)	high-dose balsalazide - oral	high-dose mesalazine - oral	hydrocortisone - topical (foam)	mesalazine - topical (foam)	mesalazine - topical (liquid enema)	low-dose balsalazide - oral	low-dose mesalazine - oral + mesalazine - topical (liquid enema)	placebo
low-dose mesalazine - oral		1.58 (0.78, 3.22)	-	1.14 (0.65, 1.99)	1.36 (1.13, 1.63)	-	-	-	1.04 (0.32, 3.33)	1.50 (0.57, 3.96)	0.46 (0.31, 0.68)
budesonide - oral	0.82 (0.58, 1.15)		-	-	1.74 (1.08, 2.81)	-	-	-	-	-	0.74 (0.51, 1.08)
budesonide - topical (foam)	1.53 (1.02, 2.32)	1.87 (1.19, 2.92)		-	-	0.94 (0.62, 1.42)	-	-	-	-	0.39 (0.28, 0.53)
high-dose balsalazide - oral	1.19 (0.78, 1.83)	1.44 (0.87, 2.41)	0.77 (0.46, 1.33)		-	-	-	-	0.84 (0.27, 2.65)	-	0.47 (0.26, 0.86)
high-dose mesalazine - oral	1.34 (1.13, 1.60)	1.64 (1.17, 2.27)	0.88 (0.58, 1.32)	1.13 (0.72, 1.77)		-	-	-	-	-	0.46 (0.32, 0.67)
hydrocortisone - topical (foam)	1.54 (0.89, 2.66)	1.87 (1.06, 3.32)	1.00 (0.67, 1.50)	1.30 (0.68, 2.47)	1.15 (0.66, 1.97)		-	-	-	-	0.27 (0.12, 0.64)
mesalazine - topical (foam)	1.40 (0.54, 3.69)	1.71 (0.65, 4.58)	0.91 (0.35, 2.45)	1.18 (0.43, 3.31)	1.04 (0.40, 2.73)	0.91 (0.32, 2.60)		-	1.40 (0.35, 5.99)	-	0.42 (0.17, 1.06)
mesalazine - topical (liquid enema)	3.16 (1.45, 7.26)	3.86 (1.74, 9.07)	2.07 (0.94, 4.87)	2.67 (1.15, 6.58)	2.35 (1.08, 5.40)	2.06 (0.87, 5.20)	2.27 (0.69, 7.61)		3.17 (0.89, 12.45)	-	0.19 (0.09, 0.40)
low-dose balsalazide - oral	1.01 (0.33, 2.75)	1.22 (0.39, 3.52)	0.65 (0.20, 1.91)	0.85 (0.28, 2.34)	0.75 (0.24, 2.07)	0.65 (0.19, 2.03)	-	-		-	-
low-dose mesalazine - oral + topical (liquid enema)	1.52 (0.56, 4.19)	1.85 (0.65, 5.38)	0.99 (0.34, 2.97)	1.28 (0.44, 3.87)	1.13 (0.41, 3.16)	0.99 (0.32, 3.16)	1.08 (0.28, 4.31)	0.48 (0.13, 1.75)	1.52 (0.36, 6.82)		-
placebo	0.59 (0.45, 0.77)	0.71 (0.52, 0.98)	0.38 (0.28, 0.52)	0.49 (0.32, 0.75)	0.44 (0.33, 0.57)	0.38 (0.24, 0.61)	0.42 (0.17, 1.04)	0.19 (0.08, 0.38)	0.59 (0.21, 1.81)	0.39 (0.13, 1.07)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% Cis derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. . ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs higher than 1 favour the column defining treatment.
Comparisons of different agents within the same class are highlighted in yellow. Comparisons of different modes of topical delivery are highlighted in blue.

Table 13: Model selection based on fixed- and random-effects for each model

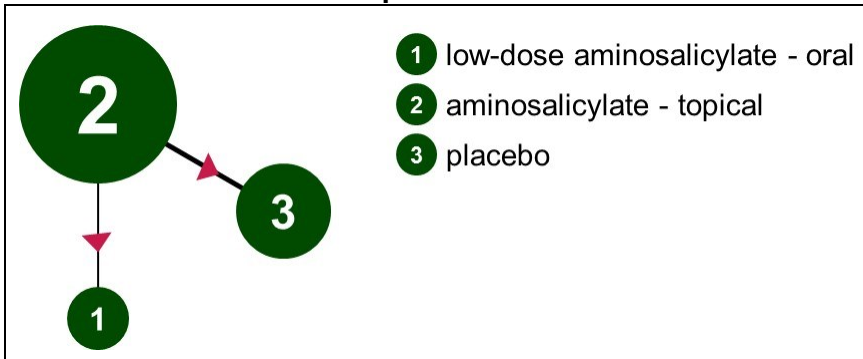
Outcome	Model	Number of Studies	Participants	Datapoints	Total residual deviance	DIC	Tau -Standard deviation of random effects distribution (95%CrI)
Proctitis							
0-2wks	FE	3	214	7	6.69	35.91	N/A
	RE	3	214	7	6.67	36.94	0.634 (0.035, 1.869)
0-4 wks	FE	4	343	9	9.56	48.65	N/A
	RE	4	343	9	8.89	49.69	0.539 (0.020, 1.807)
5-8 wks	FE	3	279	8	11.13	44.23	N/A
	RE	3	279	8	8.57	43.42	0.697 (0.058, 1.864)
Proctosigmoiditis and left-sided							
0-2wks	FE	2	201	5	4.23	26.44	N/A
	RE	Random effects model not possible[a].					
0-4 wks	FE	8	1356	18	19.02	96.99	N/A
	RE	8	1356	18	17.49	97.40	0.737 (0.033, 1.872)
5-8 wks	FE	23	5675	58	62.31	351.8	N/A
	RE	23	5675	58	59.06	353.3	0.121 (0.005, 0.354)
Extensive							
0-4wks	FE	3	188	6	6.108	34.66	N/A
	RE	Random effects model not possible[b].					
5-8 wks	FE	4	331				
	RE	4	331				
Withdrawal due to adverse events – all extents of disease							
All follow-up	FE	28	6594	67	68.99	303.98	n/a
All follow-up	RE	28	6594	67	64.96	303.26	0.213 (0.007, 0.638)

[a] Random effects model not possible as there are no loops in the network and no links with more than 2 studies.
[b] Random effects model not possible as there are no loops in the network and no links with more than 2 studies. Additionaly, in order to connect the network, the network borrows evidence from proctosigmoiditis and left-sided extent of disease at 0-4 weeks follow-up.

I.3 Results

I.3.1 Clinical remission

I.3.1.1 Proctitis: 2 weeks' follow-up



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 8: Proctitis; clinical remission at 2 weeks; mode, dose and class – evidence network

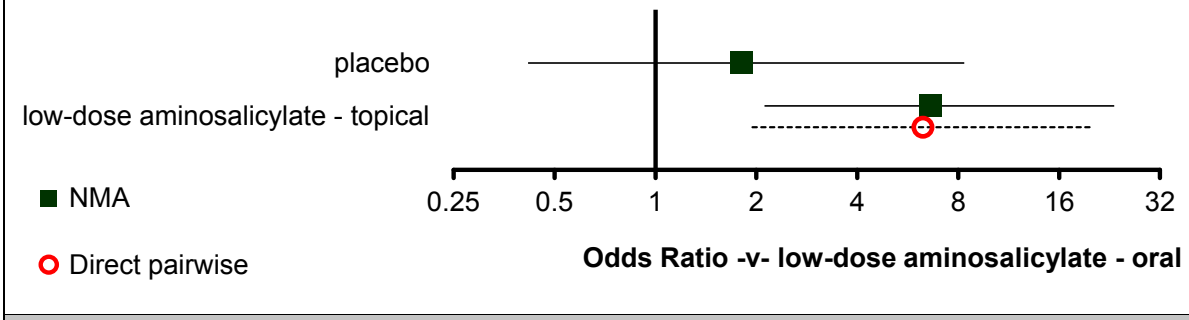
Table 14: Proctitis; clinical remission at 2 weeks; mode, dose and class – input data

	low-dose aminosalicylate - oral	aminosalicylate - topical	placebo
Campieri et al. (1990)		27/63	7/31
Gionchetti et al. (1998)	6/29	18/29	
Campieri et al. (1990a)		8/32	1/30

Table 15: Proctitis; clinical remission at 2 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	aminosalicylate - topical	placebo
low-dose aminosalicylate - oral		6.27 (1.95, 20.22)	-
aminosalicylate - topical	6.62 (2.11, 23.38)		0.29 (0.12, 0.69)
placebo	1.81 (0.42, 8.35)	0.27 (0.11, 0.64)	

Values given are odds ratios.
. The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

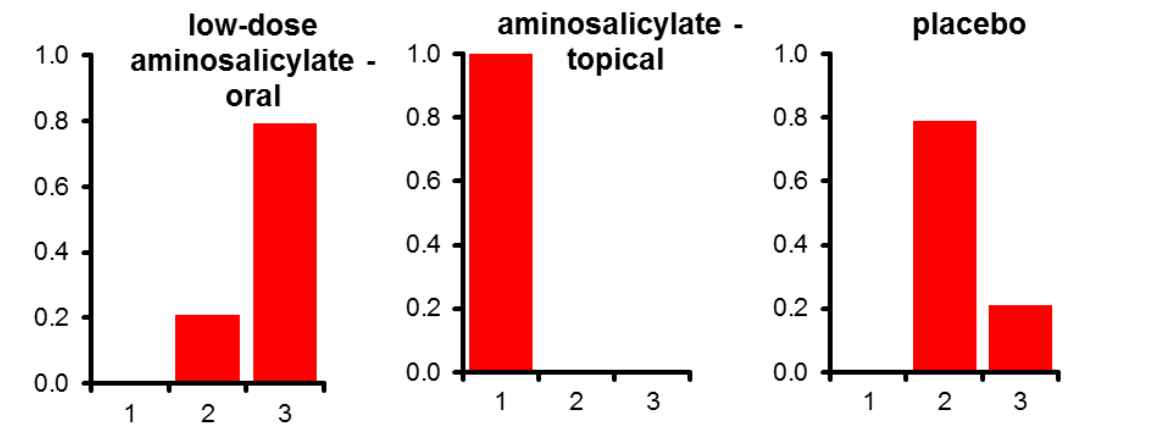


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 9: Proctitis; clinical remission at 2 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 16: Proctitis mode, dose and class fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.000	3 (2, 3)
aminosalicylate - topical	0.999	1 (1, 1)
placebo	0.001	2 (2, 3)



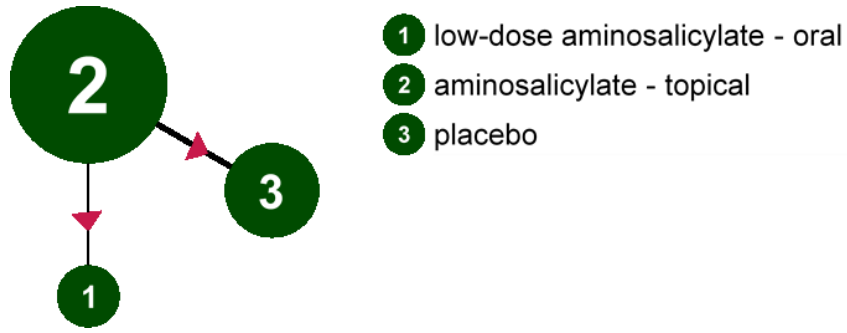
Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 10: Proctitis; clinical remission at 2 weeks; mode, dose and drug/class; fixed-effect – rank probability histograms

Table 17: Proctitis mode, dose and class fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
6.675 (compared to 7 datapoints)	30.842	25.803	5.038	35.88

I.3.1.2 Proctitis: 0 to 4 weeks' follow-up



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 11: Proctitis; clinical remission at 0–4 weeks; mode, dose and class – evidence network

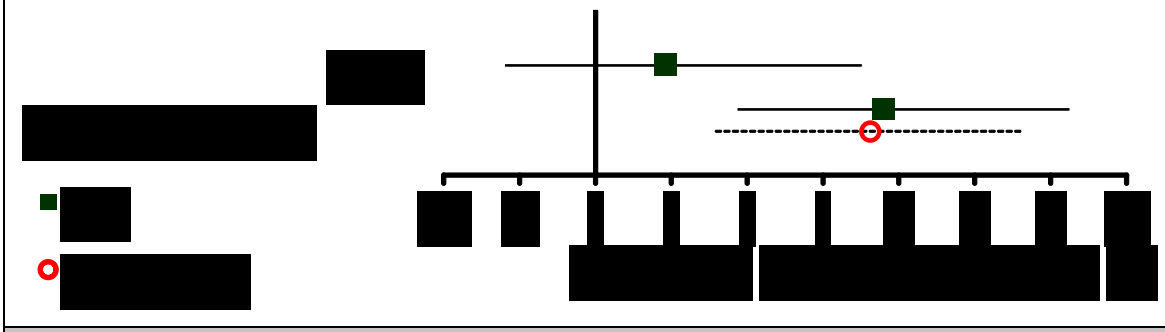
Table 18: Proctitis; clinical remission at 0–4 weeks; mode, dose and class – input data

	low-dose aminosalicylate - oral	aminosalicylate - topical	placebo
Campieri et al. (1990)		45/63	12/31
Gionchetti et al. (1998)	12/29	26/29	
Watanabe et al. (2013)		41/65	11/64
Campieri et al. (1990)		18/32	2/30

Table 19: Proctitis; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	aminosalicylate - topical	placebo
low-dose aminosalicylate - oral		12.28 (3.01, 50.04)	-
aminosalicylate - topical	13.99 (3.68, 75.81)		0.14 (0.08, 0.25)
placebo	1.91 (0.44, 11.35)	0.14 (0.08, 0.23)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

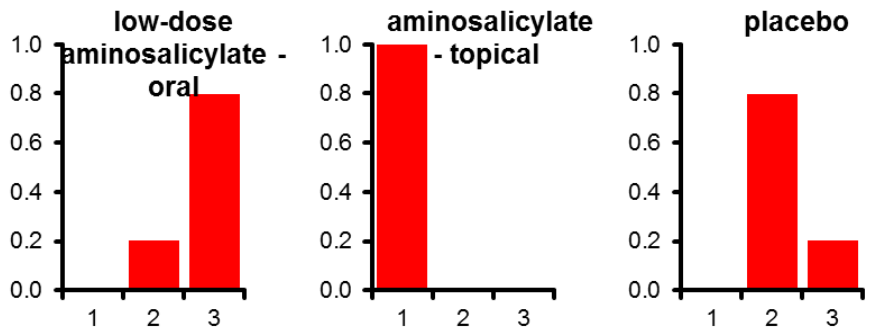


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 12: Proctitis; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 20: Proctitis; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.000	3 (2, 3)
aminosalicylate - topical	1.000	1 (1, 1)
placebo	0.000	2 (2, 3)



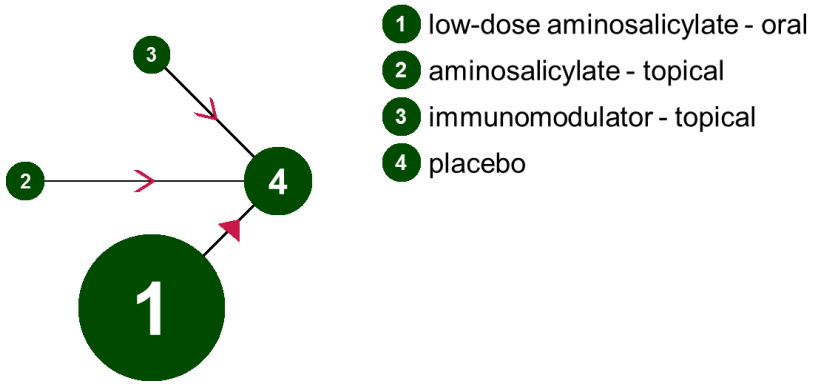
Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 13: Proctitis; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – rank probability histograms

Table 21: Proctitis; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
9.581 (compared to 9 datapoints)	42.637	36.585	6.052	48.689

I.3.1.3 Proctitis: 5 to 8 weeks' follow-up



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 14: Proctitis; clinical remission at 5–8 weeks; mode, dose and class – evidence network

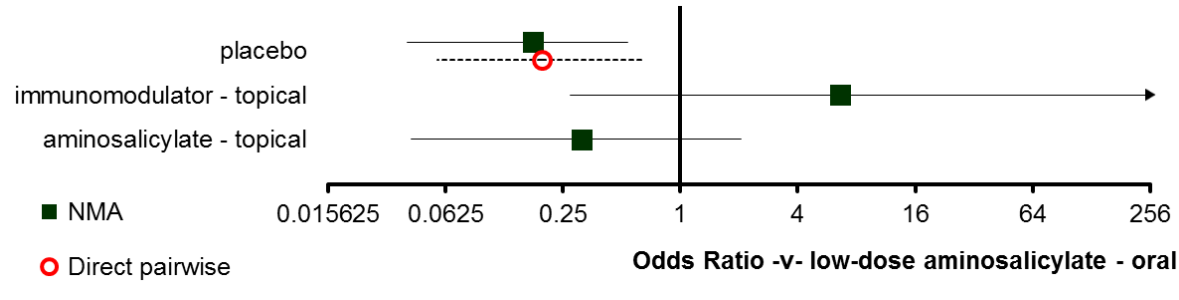
Table 22: Proctitis; clinical remission at 5–8 weeks; mode, dose and class – input data

	low-dose aminosalicylate - oral	aminosalicylate - topical	immunomodulator - topical	placebo
Ito et al. (2010)	67/193			3/32
Pokrotnieks et al. (2000)		7/13		8/20
Lawrance et al. (2017)			5/11	0/10

Table 23: Proctitis; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	aminosalicylate - topical	immunomodulator - topical	placebo
low-dose aminosalicylate - oral		-	-	0.19 (0.06, 0.66)
aminosalicylate - topical	0.31 (0.04, 2.05)		-	0.57 (0.14, 2.34)
immunomodulator - topical	6.59 (0.27, 3661.00)	21.90 (0.80, 12000.00)		0.06 (0.00, 1.20)
placebo	0.18 (0.04, 0.54)	0.55 (0.13, 2.34)	0.03 (0.00, 0.45)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

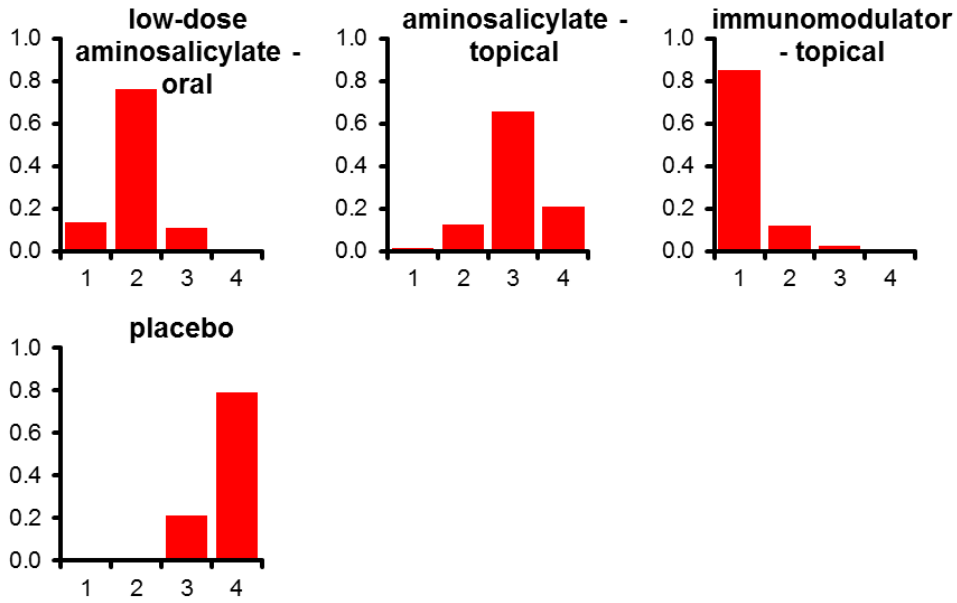


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 15: Proctitis; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 24: Proctitis; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.134	2 (1, 3)
aminosalicylate - topical	0.014	3 (2, 4)
immunomodulator - topical	0.852	1 (1, 3)
placebo	0.000	4 (3, 4)



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 16: Proctitis; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – rank probability histograms

Table 25: Proctitis; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
11.13 (compared to 8 datapoints)	38.381	32.525	5.856	44.237

I.3.1.4 Proctosigmoiditis and left-sided: 2 weeks' follow-up

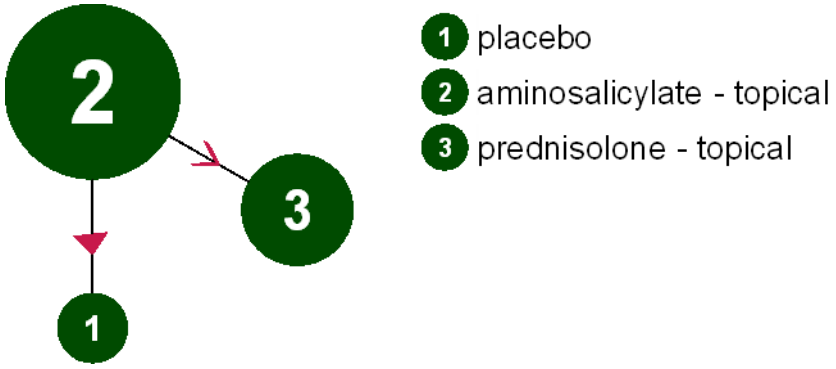


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Figure 17: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class – evidence network

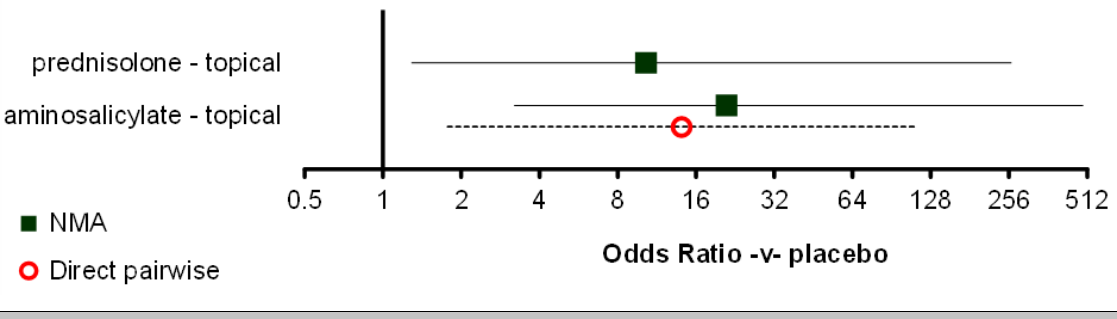
Table 26: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class – input data

	placebo	aminosalicylate - topical	prednisolone - topical
Binder et al. (1987)		27/56	19/61
Campieri et al. (1991)	1/27	20/57	

Table 27: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	placebo	aminosalicylate - topical	prednisolone - topical
placebo		14.05 (1.77, 111.38)	-
aminosalicylate - topical	21.04 (3.20, 492.60)		0.49 (0.23, 1.03)
prednisolone - topical	10.30 (1.29, 260.90)	0.48 (0.22, 1.03)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

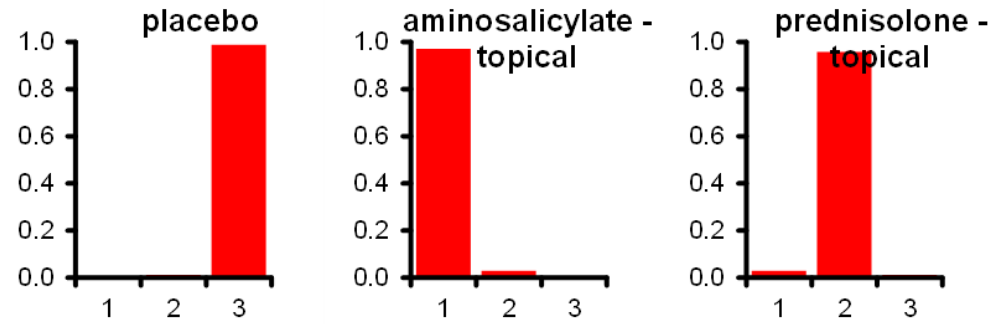


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 18: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 28: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
placebo	0.000	3 (3, 3)
aminosalicylate - topical	0.971	1 (1, 2)
prednisolone - topical	0.029	2 (1, 2)



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 19: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class; fixed-effect – rank probability histograms

Table 29: Proctosigmoiditis and left-sided; clinical remission at 2 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
4.228 (compared to 5 datapoints)	22.543	18.647	3.896	26.439

I.3.1.5 Proctosigmoiditis and left-sided: 0 to 4 weeks' follow-up

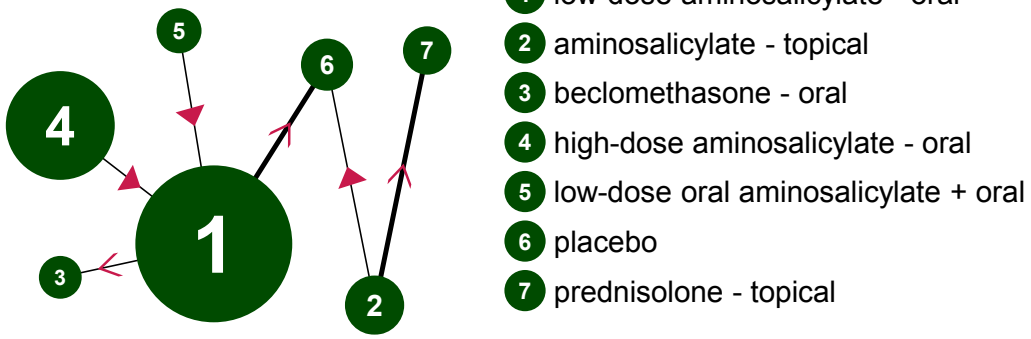


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Figure 20: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class – evidence network

Table 30: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class – input data

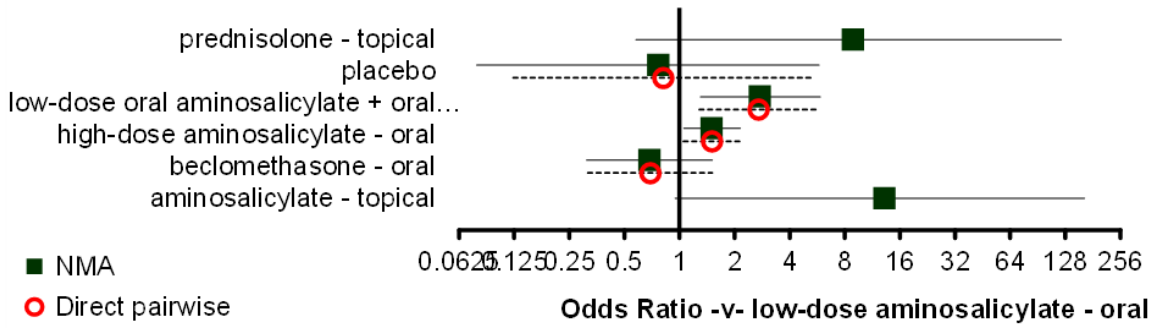
	low-dose aminosalicylate - oral	aminosalicylate - topical	beclomethasone - oral	high-dose aminosalicylate - oral	low-dose oral aminosalicylate + oral	placebo	prednisolone - topical
Binder et al. (1987)		27/56					19/61
Campieri et al. (1991)		37/57				3/27	
Lauritsen et al. (1986)		7/13					9/11
Sandborn et al. (2009)	65/359			91/365			
Sninsky et al. (1991)	2/106					1/52	
Campieri et al. (2003)	41/62		27/47				
Pontes et al. (2014)	1/8					1/13	
Rizzello et al. (2002)	21/61				34/58		

Table 31: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	aminosalicylate - topical	beclomethasone - oral	high-dose aminosalicylate - oral	low-dose oral aminosalicylate + oral beclomethasone	placebo	prednisolone - topical
low-dose aminosalicylate - oral		-	0.69 (0.32, 1.51)	1.50 (1.05, 2.15)	2.70 (1.28, 5.67)	0.81 (0.12, 5.36)	-

	low-dose aminosalicylate - oral	aminosalicylate - topical	beclomethasone - oral	high-dose aminosalicylate - oral	low-dose oral aminosalicylate + oral beclomethasone	placebo	prednisolone - topical
aminosalicylate - topical	13.21 (0.95, 163.50)		-	-	-	0.07 (0.02, 0.25)	0.68 (0.35, 1.33)
beclomethasone - oral	0.69 (0.31, 1.52)	0.05 (0.00, 0.81)		-	-	-	-
high-dose aminosalicylate - oral	1.50 (1.06, 2.16)	0.11 (0.01, 1.62)	2.19 (0.92, 5.22)		-	-	-
low-dose oral aminosalicylate + oral beclomethasone	2.75 (1.30, 5.89)	0.21 (0.01, 3.26)	4.01 (1.33, 12.00)	1.83 (0.79, 4.23)		-	-
placebo	0.77 (0.08, 5.80)	0.06 (0.01, 0.20)	1.12 (0.10, 9.49)	0.51 (0.05, 3.87)	0.28 (0.03, 2.36)		-
prednisolone - topical	8.88 (0.58, 122.00)	0.67 (0.33, 1.34)	12.95 (0.77, 200.10)	5.90 (0.37, 82.59)	3.24 (0.19, 49.52)	11.50 (2.72, 63.97)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

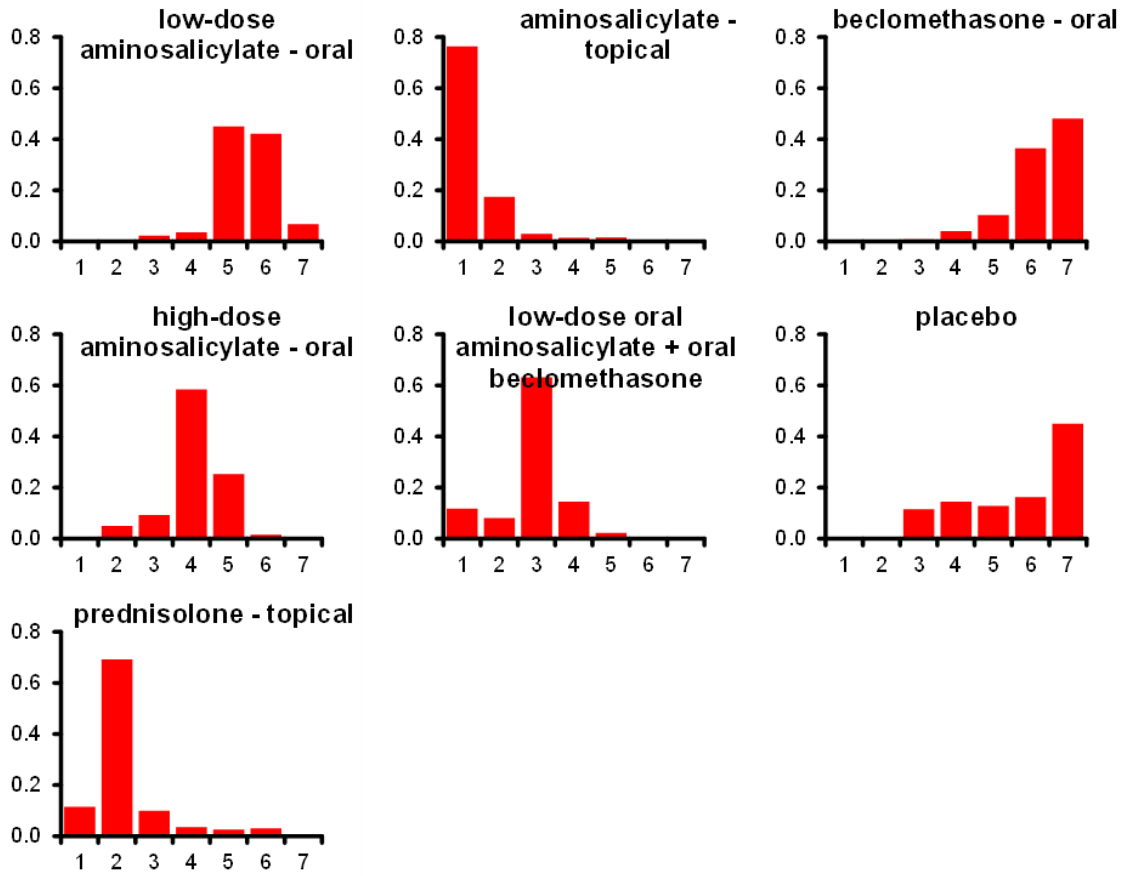


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 21: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 32: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.000	5 (4, 7)
aminosalicylate - topical	0.764	1 (1, 4)
beclomethasone - oral	0.000	6 (4, 7)
high-dose aminosalicylate - oral	0.004	4 (2, 5)
low-dose oral aminosalicylate + oral beclomethasone	0.117	3 (1, 5)
placebo	0.000	6 (3, 7)
prednisolone - topical	0.115	2 (1, 6)



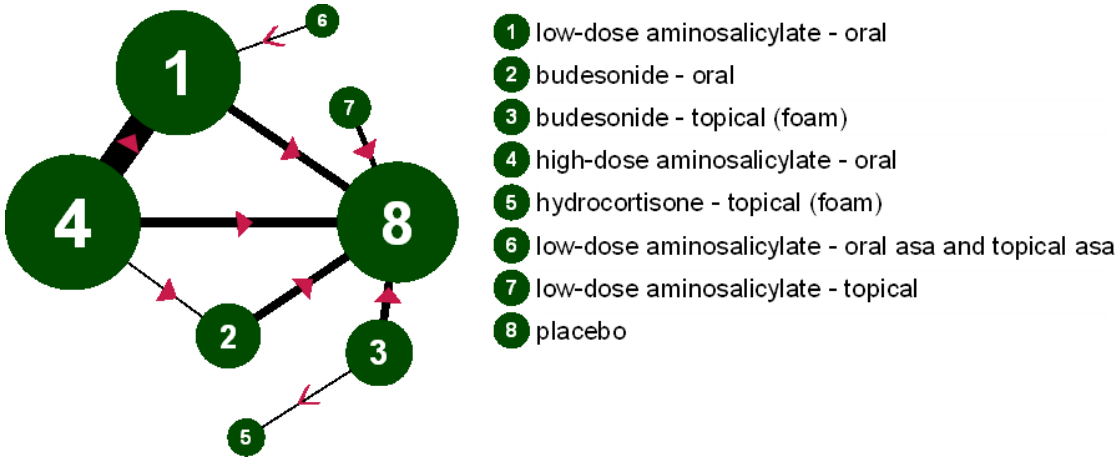
Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 22: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – rank probability histograms

Table 33: Proctosigmoiditis and left-sided; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
19.02 (compared to 18 datapoints)	83.053	69.116	13.937	96.991

I.3.1.6 Proctosigmoiditis and left-sided: 5 to 8 weeks' follow-up



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 23: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class – evidence network

Table 34: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class – input data

	low-dose aminosalicylate - oral	budesonide - oral	budesonide - topical (foam)	high-dose aminosalicylate - oral	hydrocortisone - topical (foam)	low-dose aminosalicylate - oral asa and topical asa	low-dose aminosalicylate - topical	placebo
Bar-Meir et al. (2003)			64/120		67/128			
D'Haens et al. (2006)	4/27			2/11				
Hanauer et al. (1993)	47/189			28/95				11/ 90
Hanauer (1998)							67/ 144	10/ 70
Hanauer et al. (2005)	23/77			25/89				
Kamm et al. (2007)	64/170			35/85				19/ 86
Kruis et al. (2003)	52/103			129/213				
Levine et al. (2002)	14/71			8/35				
Pokrotnieks et al. (2000)							23/41	13/ 37

	low-dose aminosalicylate - oral	budesonide - oral	budesonide - topical (foam)	high-dose aminosalicylate - oral	hydrocortisone - topical (foam)	low-dose aminosalicylate - oral asa and topical asa	low-dose aminosalicylate - topical	placebo
Pruitt et al. (2002)	38/77			38/73				
Sandborn et al. (2009)	121/347			152/353				
Sandborn et al. (2012)		18/66						7/75
Scherl et al. (2009)				64/166				19/83
Sninsky et al. (1991)	12/106							2/52
Vecchi et al. (2001)	55/67					55/3		
Travis S et al. (2013)		17/95						6/108
Feagan et al. (2013)				42/140				29/141
Sandborn et al. (2015)			110/267					67/279
Naganuma et al. (2016)			55/111					11/54
Suzuki et al. (2016)	10/55			14/55				
Naganuma et al. (2017)			26/64					10/62
Rubin David et al. (2017)		56/230						52/228
Gross et al. (2011)		56/140		72/134				
Ogata et al. (2017)	40/131			56/136				

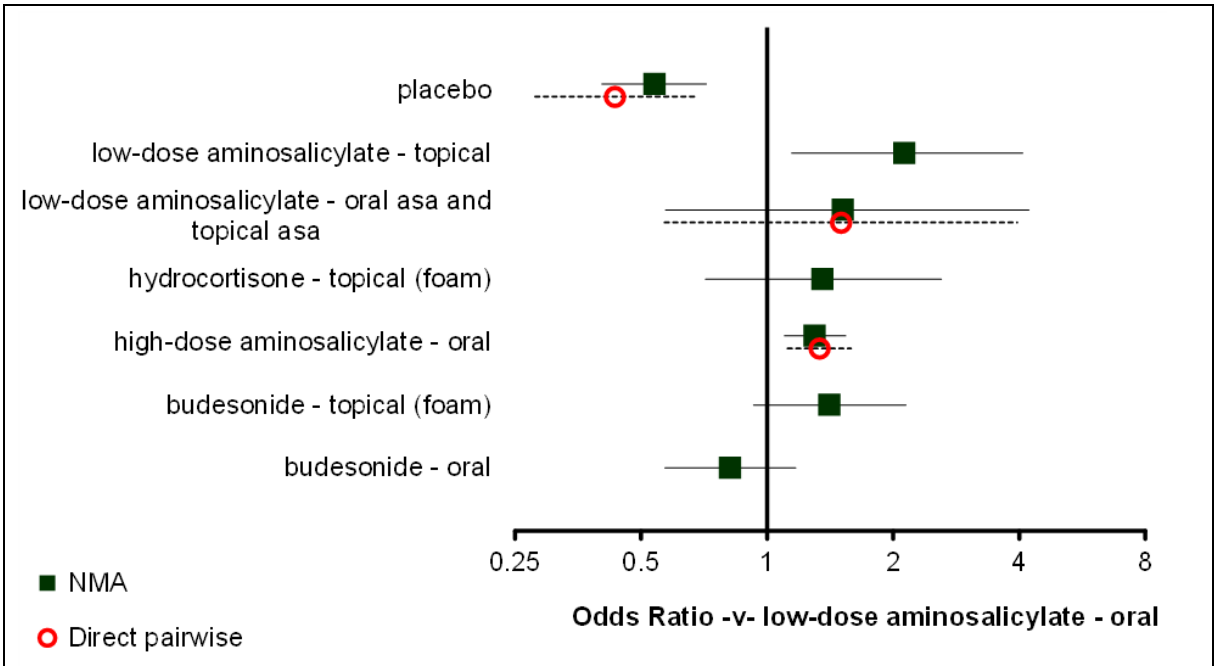
Table 35: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	budesonide - oral	budesonide - topical (foam)	high-dose aminosalicylate - oral	hydrocortisone - topical (foam)	low-dose aminosalicylate - oral asa and topical asa	low-dose aminosalicylate - topical	placebo
low-dose aminosalicylate - oral		-	-	1.33 (1.12, 1.58)	-	1.50 (0.57, 3.96)	-	0.43 (0.28, 0.67)

	low-dose aminosalicylate - oral	budesonide - oral	budesonide - topical (foam)	high-dose aminosalicylate - oral	hydrocortisone - topical (foam)	low-dose aminosalicylate - oral asa and topical asa	low-dose aminosalicylate - topical	placebo
budesonide - oral	0.82 (0.57, 1.17)		-	1.74 (1.08, 2.81)	-	-	-	0.63 (0.44, 0.90)
budesonide - topical (foam)	1.41 (0.93, 2.15)	1.73 (1.13, 2.66)		-	0.96 (0.58, 1.58)	-	-	0.38 (0.28, 0.52)
high-dose aminosalicylate - oral	1.30 (1.10, 1.54)	1.59 (1.14, 2.22)	0.92 (0.62, 1.38)		-	-	-	0.47 (0.34, 0.64)
hydrocortisone - topical (foam)	1.36 (0.71, 2.61)	1.66 (0.87, 3.20)	0.96 (0.58, 1.58)	1.04 (0.55, 1.99)		-	-	-
low-dose aminosalicylate - oral asa and topical asa	1.52 (0.57, 4.22)	1.87 (0.66, 5.54)	1.08 (0.38, 3.25)	1.17 (0.44, 3.32)	1.13 (0.35, 3.75)		-	-
low-dose aminosalicylate - topical	2.13 (1.15, 4.08)	2.60 (1.39, 5.02)	1.51 (0.80, 2.94)	1.64 (0.89, 3.14)	1.57 (0.70, 3.61)	1.40 (0.42, 4.51)		0.26 (0.14, 0.45)
placebo	0.54 (0.40, 0.72)	0.66 (0.49, 0.89)	0.38 (0.28, 0.52)	0.42 (0.32, 0.54)	0.40 (0.22, 0.71)	0.35 (0.12, 0.97)	0.25 (0.14, 0.44)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

Figure 24: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

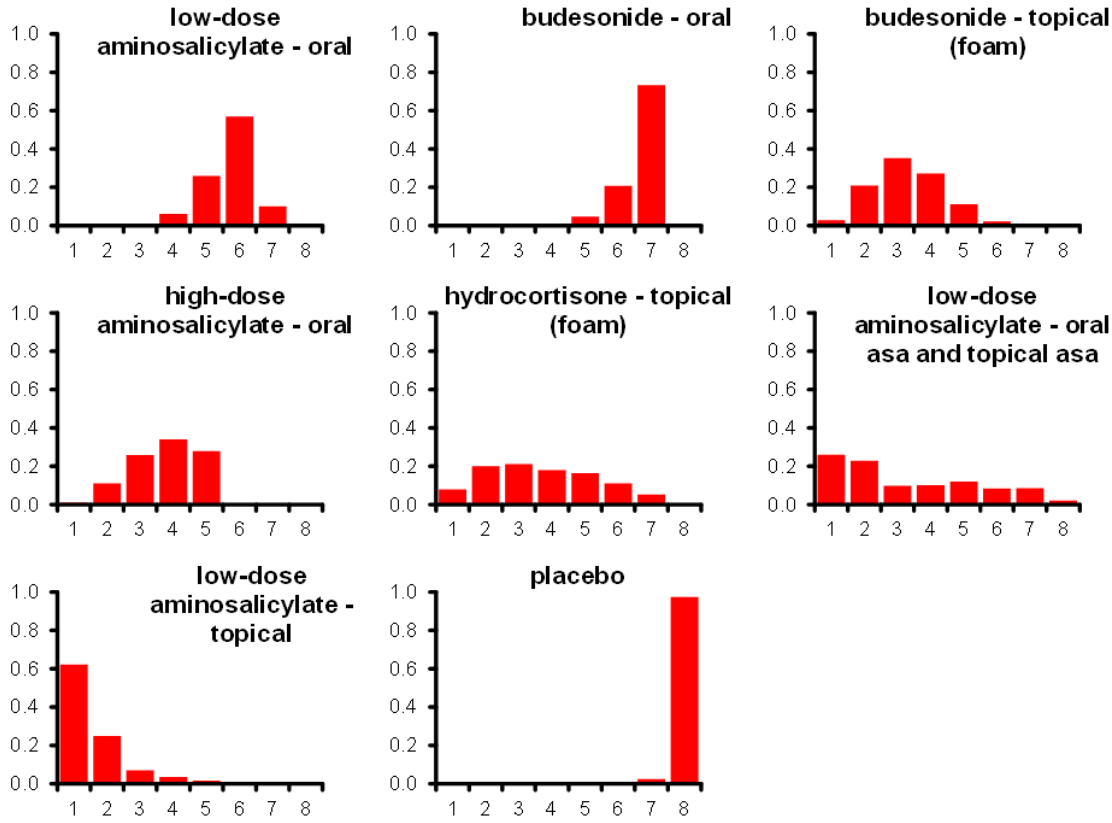


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 25: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 36: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.000	6 (4, 7)
budesonide - oral	0.000	7 (5, 7)
budesonide - topical (foam)	0.028	3 (1, 5)
high-dose aminosalicylate - oral	0.010	4 (2, 5)
hydrocortisone - topical (foam)	0.079	4 (1, 7)
low-dose aminosalicylate - oral asa and topical asa	0.260	3 (1, 7)
low-dose aminosalicylate - topical	0.622	1 (1, 4)
placebo	0.000	8 (7, 8)



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 26: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – rank probability histograms

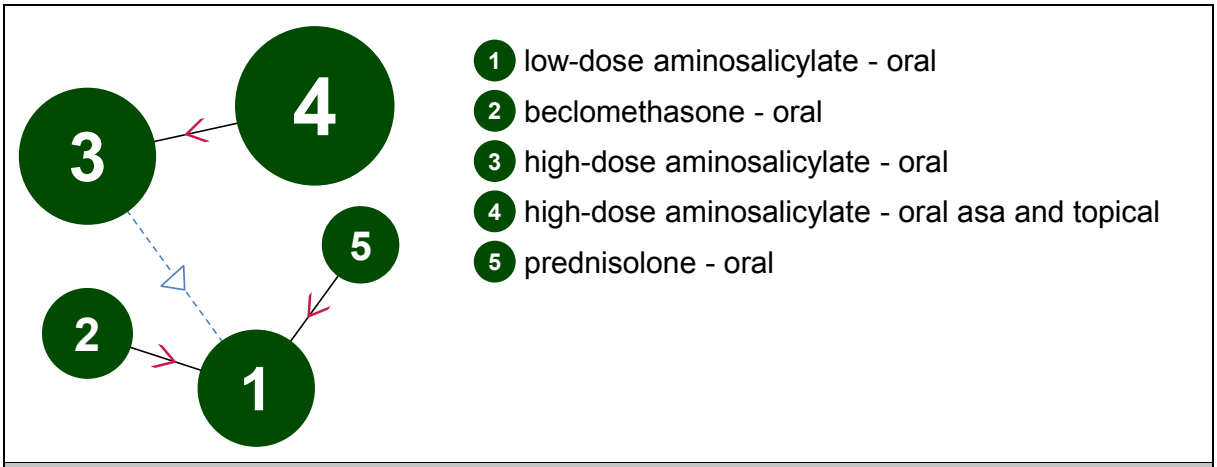
Table 37: Proctosigmoiditis and left-sided; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
62.98 (compared to 58 datapoints)	323.252	292.229	31.023	354.276

I.3.1.7 Extensive disease in adults: 0 to 4 weeks' follow-up

Examination of available data for extensive disease in adults at 0–4 weeks' follow-up showed that it was not possible to form a single, connected network of evidence. Two disconnected networks were present: 1 comparing high-dose oral aminosalicylate monotherapy with combined high-dose oral aminosalicylate and topical aminosalicylate, and 1 comparing low-dose oral aminosalicylates with oral prednisolone and oral beclometasone. In order to connect these 2 networks, it was necessary to make an assumption about the relationship between them (see NICE DSU TSD1). The committee advised that, although absolute probabilities of remission are expected to be different between extensive disease and proctosigmoiditis/left-sided disease, at the level of relative effects a similar difference could be expected between low- and high-dose oral aminosalicylates. Therefore, the posterior mean and variance of this contrast from the proctosigmoiditis/left-sided disease NMA (that is, the log-odds ratio of remission with high-dose aminosalicylates, compared with low-dose

aminosalicylates) was entered into the network as data (assuming normality on a log-odds scale), enabling the estimation of all other relevant contrasts.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.
The dashed blue line shows where evidence from proctosigmoiditis/left-sided disease has been used in order to form a connected network.

Figure 27: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class – evidence network

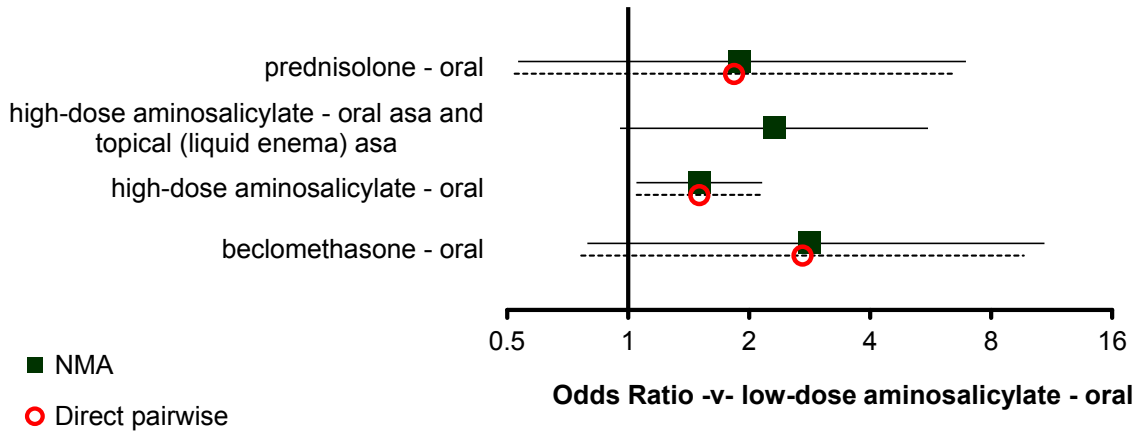
Table 38: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class – input data

	low-dose aminosalicylate - oral	beclometasone - oral	high-dose aminosalicylate - oral	high-dose aminosalicylate - oral asa and topical asa	prednisolone - oral
Lennard Jones et al. (1960)	8/20				11/20
Campieri et al. (2003)	9/18	19/26			
Probert et al. (2014)			16/47	25/57	

Table 39: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	beclometasone - oral	high-dose aminosalicylate - oral	high-dose aminosalicylate - oral and topical asa	prednisolone - oral
low-dose aminosalicylate - oral		2.71 (0.76, 9.63)	*1.50 (1.05, 2.15)*	-	1.83 (0.52, 6.43)
beclomethasone - oral	2.83 (0.79, 10.86)		-	-	-
high-dose aminosalicylate - oral	*1.51 (1.06, 2.16)*	0.53 (0.13, 2.01)		1.51 (0.68, 3.36)	-
high-dose aminosalicylate - oral and topical (liquid enema) asa	2.31 (0.95, 5.57)	0.81 (0.16, 3.86)	1.53 (0.69, 3.43)		-
prednisolone - oral	1.89 (0.53, 6.92)	0.66 (0.10, 4.09)	1.26 (0.33, 4.78)	0.82 (0.18, 3.92)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.Estimates shown in italics are not estimated in this model; rather they are assumed identical to observed effect in the analogous NMA for proctosigmoiditis and left-sided disease, in order to join what would otherwise be a disconnected network.

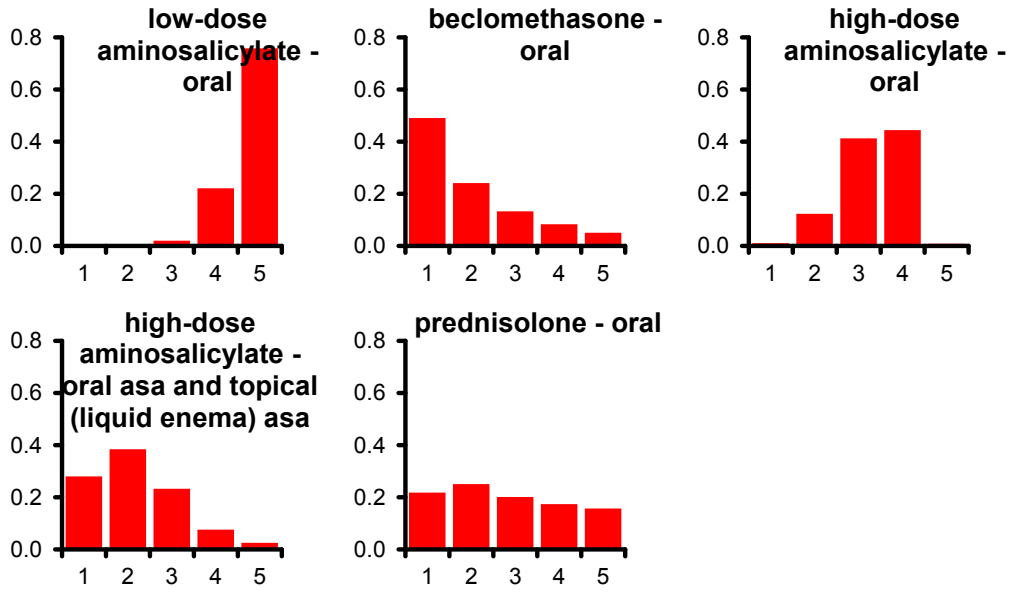


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 28: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 40: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.000	5 (4, 5)
beclometasone - oral	0.491	2 (1, 5)
high-dose aminosalicylate - oral	0.011	3 (2, 4)
high-dose aminosalicylate - oral asa and topical (liquid enema) asa	0.280	2 (1, 5)
prednisolone - oral	0.218	3 (1, 5)



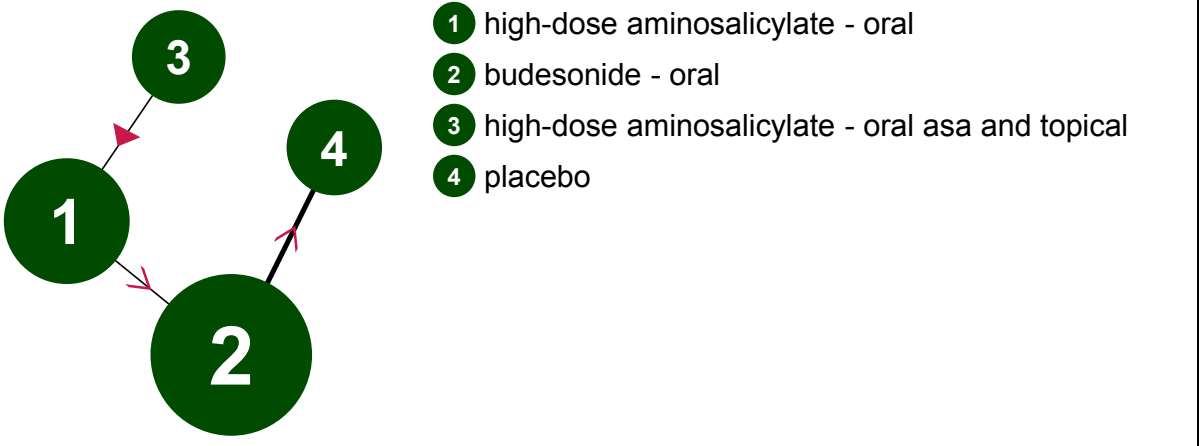
Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 29: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – rank probability histograms

Table 41: Extensive disease in adults; clinical remission at 0–4 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
6.108 (compared to 6 datapoints)	28.565	22.474	6.091	34.655

I.3.1.8 Extensive disease in adults: 5 to 8 weeks' follow-up



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 30: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class – evidence network

Table 42: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class – input data

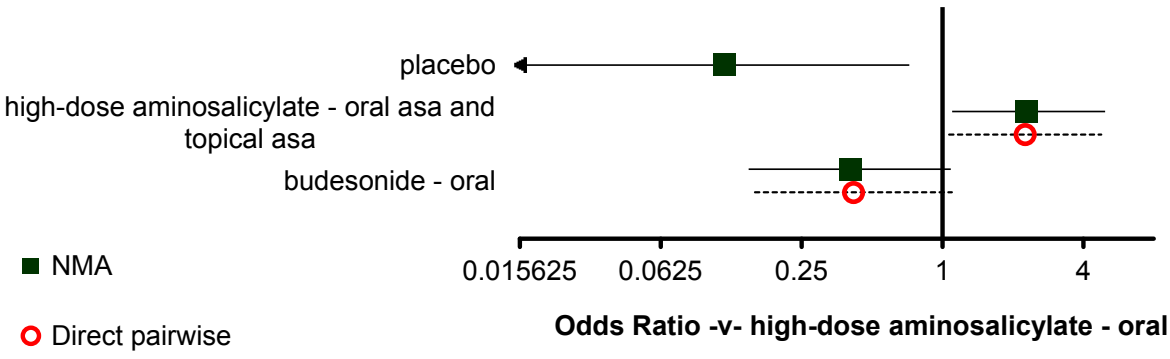
	high-dose aminosalicylate - oral	budesonide - oral	high-dose aminosalicylate - oral asa and topical asa	placebo
Sandborn et al. (2012)		4/56		2/40
Travis S et al. (2013)		4/31		0/20
Probert et al. (2014)	25/57		37/58	
Gross et al. (2011)	19/32	14/37		

Table 43: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	high-dose aminosalicylate - oral	budesonide - oral	high-dose aminosalicylate - oral asa and topical asa	placebo
high-dose aminosalicylate - oral		0.42 (0.16, 1.10)	2.26 (1.07, 4.77)	-
budesonide - oral	0.41 (0.15, 1.09)		-	0.40 (0.09, 1.70)

	high-dose aminosalicylate - oral	budesonide - oral	high-dose aminosalicylate - oral asa and topical asa	placebo
high-dose aminosalicylate - oral asa and topical asa	2.29 (1.10, 4.95)	5.66 (1.65, 19.91)		-
placebo	0.12 (0.01, 0.72)	0.29 (0.04, 1.32)	0.05 (0.00, 0.37)	

Values given are odds ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells gives pooled direct evidence from fixed-effect pairwise meta-analysis, where available (column versus row). Numbers in parentheses are 95% confidence intervals. ORs lower than 1 favour the row defining treatment, ORs higher than 1 favour the column defining treatment.

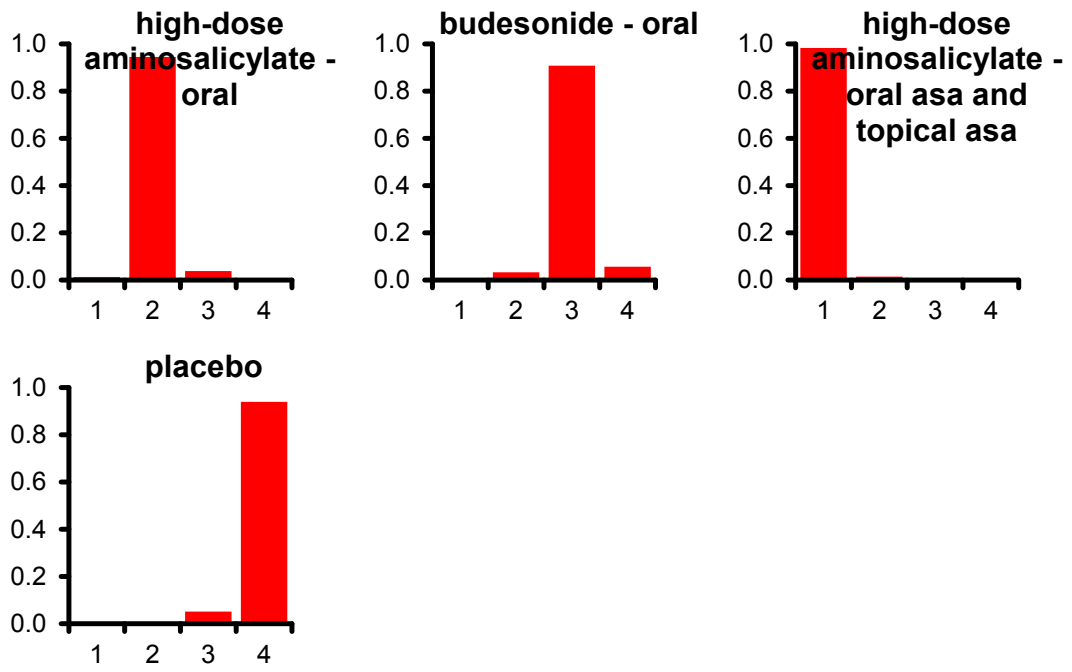


Values less than 1 favour high-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence intervals.

Figure 31: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 44: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
high-dose aminosalicylate - oral	0.013	2 (2, 3)
budesonide - oral	0.002	3 (2, 4)
high-dose aminosalicylate - oral asa and topical asa	0.983	1 (1, 1)
placebo	0.001	4 (3, 4)



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

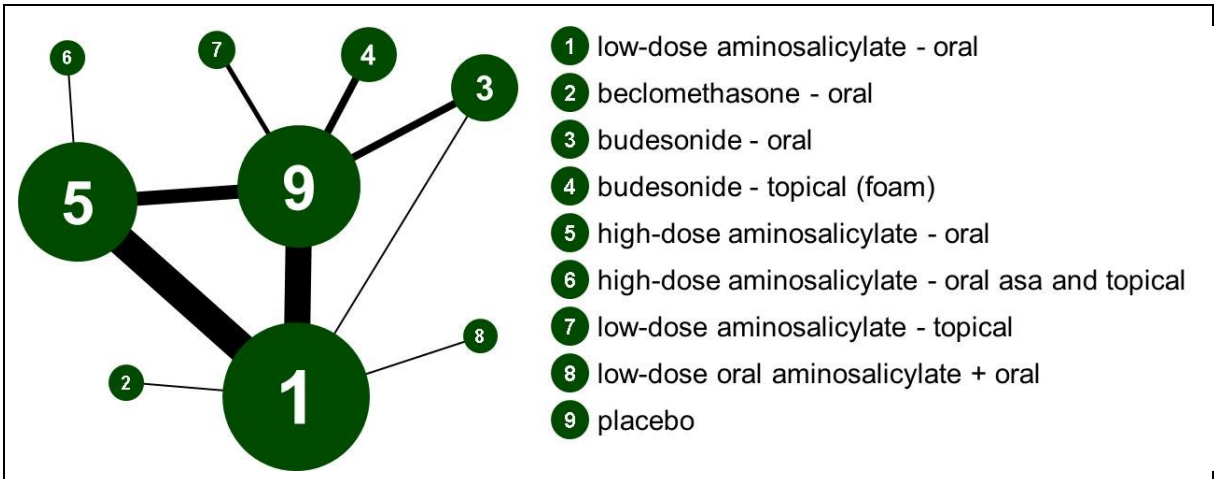
Figure 32: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – rank probability histograms

Table 45: Extensive disease in adults; clinical remission at 5–8 weeks; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
9.486 (compared to 8 datapoints)	35.214	28.303	6.911	42.125

I.3.2 Withdrawal due to adverse events

I.3.2.1 All extents of disease



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Direction and strength of effect in pairwise data is not depicted, as there is no simple way to provide a pairwise frequentist estimate of effect for this (complementary log–log) model.

Figure 33: All extents: rate of withdrawal due to adverse events; mode, dose and class – evidence network

Table 46: All extents: rate of withdrawal due to adverse events; mode, dose and class – input data

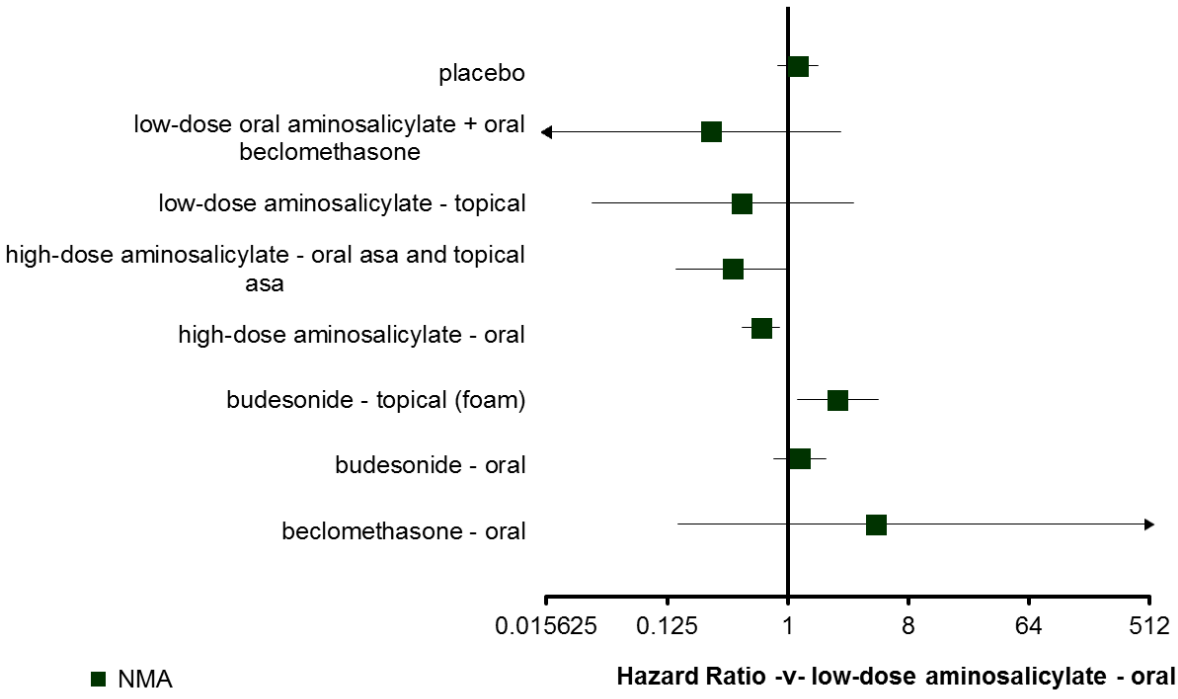
	low-dose aminosalicylate - oral	beclometasone - oral	budesonide - oral	budesonide - topical	high-dose aminosalicylate - oral	high-dose aminosalicylate - oral asa and topical asa	aminosalicylate - topical	low-dose oral aminosalicylate + oral corticosteroid	placebo
Campieri et al. (2003) - 0.08yr	0/80	1/90							
Connolly et al. (2009) - 0.15yr					11/56	9/71			
DICK A et al. (1964) - 0.08yr	2/21								0/23
Feagan et al. (2013) - 0.19yr					12/140				30/141
Feurle et al. (1989) - 0.08yr	3/52								0/53
Hanauer et al. (1993) - 0.15yr	14/189				7/95				11/90
Hanauer et al. (2005) - 0.11yr	4/139				4/129				
Hanauer et al. (2007) - 0.11yr	8/154				5/147				
Hetzel et al. (1986) - 0.11yr	2/15								4/15
Ito et al. (2010) - 0.15yr	10/196								0/33
Kamm et al. (2007) - 0.15yr	2/170				0/85				2/86
Levine et al. (2002) - 0.15yr	10/101				1/53				
Naganuma et al. (2016) - 0.11yr				2/111					2/54
Naganuma et al. (2017) - 0.11yr				4/64					2/62
Ogata et al. (2017) - 0.15yr	17/140				8/140				

	low-dose aminosalicylate - oral	beclometasone - oral	budesonide - oral	budesonide - topical	high-dose aminosalicylate - oral	high-dose aminosalicylate - oral asa and topical asa	aminosalicylate - topical	low-dose oral aminosalicylate + oral corticosteroid	placebo
Pokrotnieks et al. (2000) - 0.11yr							1/54		1/57
Pruitt et al. (2002) - 0.15yr	6/89				3/84				
Rizzello et al. (2002) - 0.08yr	3/61							1/58	
Rubin David et al. (2017) - 0.15yr			12/255						9/255
Sandborn et al. (2009) - 0.11yr	15/383				15/389				
Sandborn et al. (2012) - 0.15yr	7/124		6/127						10/129
Sandborn et al. (2015) - 0.11yr				26/268					12/278
Scherl et al. (2009) - 0.15yr					15/166				10/83
Schroeder et al. (1987) - 0.11yr	1/11				1/38				2/38
Sninsky et al. (1991) - 0.11yr	2/106								0/52
Suzuki et al. (2016) - 0.15yr	1/55				1/55				
Travis S et al. (2013) - 0.15yr			2/127						1/128
Watanabe et al. (2013) - 0.08yr							0/65		2/64

Table 47: All extents: rate of withdrawal due to adverse events; mode, dose and class; fixed-effect – relative effectiveness of all pairwise combinations

	low-dose aminosalicylate - oral	beclometasone - oral	budesonide - oral	budesonide - topical	high-dose aminosalicylate - oral	high-dose aminosalicylate - oral asa and topical asa	aminosalicylate - topical	low-dose oral aminosalicylate + oral corticosteroid	placebo
low-dose aminosalicylate - oral		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
beclometasone - oral	4.58 (0.15, 2590.00)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
budesonide - oral	1.11 (0.57, 2.16)	0.24 (0.00, 7.92)		N/A	N/A	N/A	N/A	N/A	N/A
budesonide - topical (foam)	2.22 (1.10, 4.57)	0.48 (0.00, 15.95)	1.99 (0.86, 4.73)		N/A	N/A	N/A	N/A	N/A
high-dose aminosalicylate - oral	0.62 (0.44, 0.86)	0.13 (0.00, 4.28)	0.55 (0.28, 1.09)	0.28 (0.14, 0.56)		N/A	N/A	N/A	N/A
high-dose aminosalicylate - oral asa and topical asa	0.38 (0.14, 0.98)	0.08 (0.00, 2.95)	0.34 (0.11, 1.04)	0.17 (0.05, 0.53)	0.62 (0.24, 1.50)		N/A	N/A	N/A
low-dose aminosalicylate - topical	0.41 (0.03, 2.91)	0.08 (0.00, 4.78)	0.37 (0.03, 2.85)	0.19 (0.01, 1.39)	0.67 (0.05, 4.74)	1.08 (0.07, 9.61)		N/A	N/A
low-dose oral aminosalicylate + oral corticosteroid	0.27 (0.01, 2.52)	0.05 (0.00, 3.56)	0.24 (0.01, 2.58)	0.12 (0.00, 1.29)	0.43 (0.01, 4.22)	0.70 (0.02, 8.01)	0.64 (0.01, 19.13)		N/A
placebo	1.12 (0.77, 1.64)	0.24 (0.00, 7.71)	1.00 (0.56, 1.85)	0.51 (0.27, 0.91)	1.81 (1.26, 2.63)	2.96 (1.12, 8.10)	2.69 (0.40, 34.80)	4.21 (0.43, 136.10)*	

Values given are hazard ratios.
The segment below and to the left of the shaded cells are posterior median odds ratios and 95% CIs derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the median odds ratios of the posterior distribution, and numbers in parentheses are 95% credible intervals. ORs lower than 1 favour the column defining treatment, ORs higher than 1 favour the row defining treatment. The segment above and to the right of the shaded cells is blank, as there is no simple way to provide a pairwise frequentist estimate of effect for this (complementary log–log) model.
**One trial (Rizzello 2002) contributed to wide credible intervals as it was the only trial contributing data for low-dose oral ASA + oral corticosteroid and due to its small sample and low event rate.*

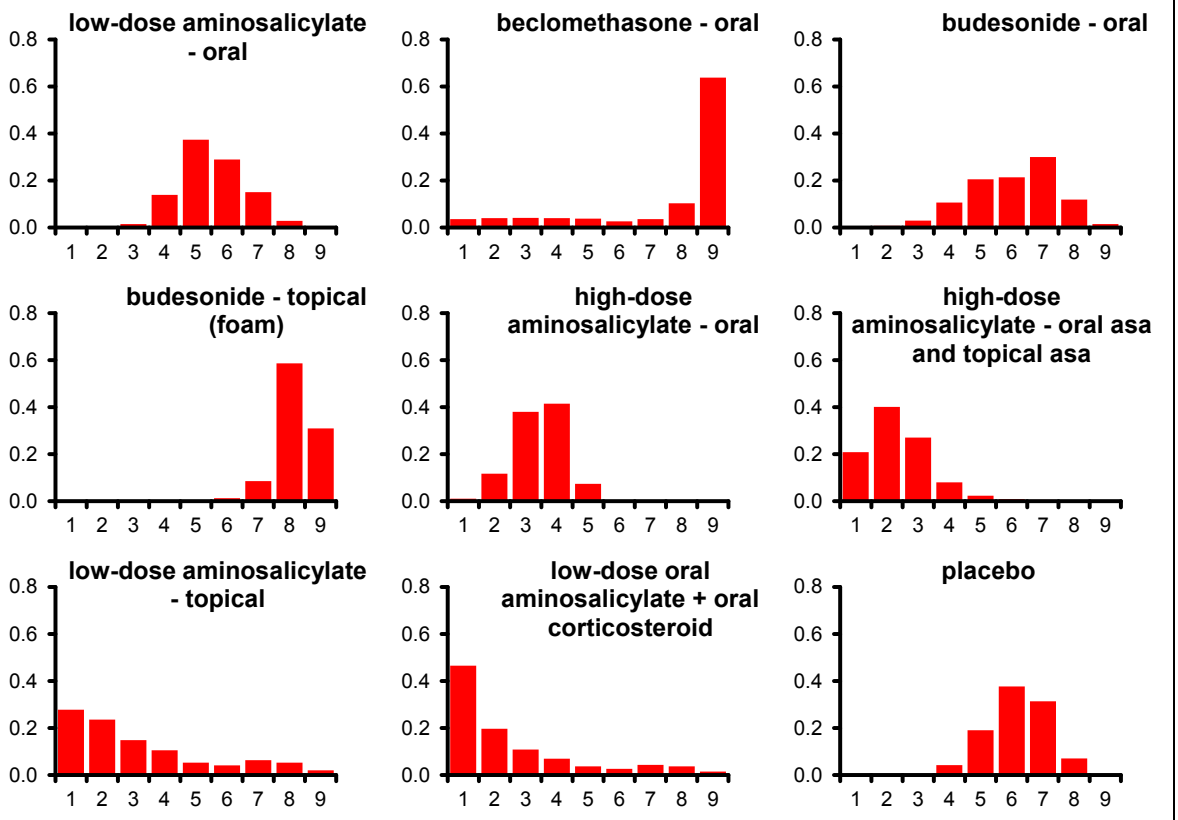


Values less than 1 favour low-dose oral aminosalicylates; values greater than 1 favour the comparator treatment. Error bars are 95% credible intervals.

Figure 34: All extents: rate of withdrawal due to adverse events; mode, dose and class; fixed-effect – relative effect of all options versus reference option

Table 48: All extents: rate of withdrawal due to adverse events; mode, dose and class; fixed-effect – rankings for each comparator

	Probability best	Median rank (95%CI)
low-dose aminosalicylate - oral	0.000	5 (4, 8)
beclometasone - oral	0.036	9 (1, 9)
budesonide - oral	0.001	6 (3, 8)
budesonide - topical (foam)	0.000	8 (7, 9)
high-dose aminosalicylate - oral	0.011	3 (2, 5)
high-dose aminosalicylate - oral asa and topical asa	0.208	2 (1, 5)
aminosalicylate - topical	0.279	2 (1, 8)
low-dose oral aminosalicylate + oral corticosteroid	0.465	2 (1, 8)
placebo	0.000	6 (4, 8)



Histograms show probability that each treatment is ranked in each position relative to the other treatments in the network. Rank 1 always refects whatever is desirable (a high probability of good outcomes or a low probability of bad outcomes).

Figure 35: All extents: rate of withdrawal due to adverse events; mode, dose and class; fixed-effectfixed-effect – rank probability histograms

Table 49: All extents: rate of withdrawal due to adverse events; mode, dose and class; fixed-effect – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
68.99 (compared to 67 datapoints)	269.107	234.236	34.87	303.977

I.4 Inconsistency checking

Inconsistency, were possible due to the presence of closed loops of direct evidence, was checked by comparing the chosen consistency model to an inconsistency model. No inconsistency was found in any of the models were inconsistency checking was possible.

I.5 WinBUGS code

Relative effects clinical remission (fixed-effect)

```
# Binomial likelihood, logit link
# Fixed-effect model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
```

```
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                              # indexes studies
  mu[i] ~ dnorm(0, .0001)                             # vague priors for all trial baselines
  for (j in 1:NumArms[i]) {                           # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])              # binomial likelihood
    logit(p[i,j]) <- mu[i] + d[Rx[i,j]] - d[Rx[i,1]] # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                  # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                      # deviance contribution
    dummy[i,j]    <- ArmNo[i,j]                       # data not used in this model
    }                                                 # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])           # summed deviance contribution
  dummy2[i]     <- Yrs[i] * RefID[i]                  # data not used in this model
  }                                                   # close study loop
totresdev     <- sum(resdev[])                        # total residual deviance

d[1]<-0                                               # effect is 0 for reference treatment
for (j in 2:NumRx) {                                  # indexes treatments
  d[j] ~ dnorm(0, .0001)                              # vague priors for treatment effects
  }                                                   # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
  }

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(lOR[c,j])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                      # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                      # probability that treat j is hth best
    }
  }
dummy3 <- YrsA                                        # data not used in this model
}
```

Relative effects clinical remission (random effects)

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                              # indexes studies
```

```
  mu[i] ~ dnorm(0, .0001)                              # vague priors for all trial baselines
  delta[i,1] <- 0                                      # effect is zero for control arm
  w[i,1] <- 0                                          # multi-arm adjustment = zero for ctrl
  for (j in 1:NumArms[i]) {                            # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])               # binomial likelihood
    logit(p[i,j]) <- mu[i] + delta[i,j]                # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                   # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                       # deviance contribution
    dummy[i,j]    <- ArmNo[i,j]                        # data not used in this model
    }                                                  # close arm loop
  for (j in 2:NumArms[i]) {                            # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])            # trial-specific LOR distributions
    md[i,j]     <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j] # mean of LOR distributions (with
multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j                      # precision of LOR distributions (with
multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]])
                                                       # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)               # cumulative adjustment for multi-arm
trials
    }
  resdev[i]     <- sum(dev[i,1:NumArms[i]])          # summed deviance contribution
  dummy2[i]     <- Yrs[i] * RefID[i]                 # data not used in this model
  }                                                    # close study loop
totresdev     <- sum(resdev[])                         # total residual deviance

d[1]<-0                                                # effect is 0 for reference treatment
for (j in 2:NumRx) {                                   # indexes treatments
  d[j] ~ dnorm(0, .0001)                               # vague priors for treatment effects
  }                                                    # close treatment loop
sd  ~  dunif(RFXpriorParam1, RFXpriorParam2)           # uniform between-trial prior
tau <- pow(sd,-2)                                      # between-trial precision



# Provide estimates of treatment effects T[k] on the natural (probability) scale
AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  logit(Tmean[j]) <- AMean + d[j]
  logit(Tpred[j]) <- APred + d[j]
  }

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lOR[c,j] <- (d[j]-d[c])
    OR[c,j]  <- exp(d[j]-d[c])
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                       # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                       # probability that treat j is hth best
    }
  }
dummy3        <- YrsA                                  # not used in this model
}
```

Relative effects withdrawal due to adverse events (fixed-effect)

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                              # indexes studies
  mu[i] ~ dnorm(0, .0001)                             # vague priors for all trial baselines
  for (j in 1:NumArms[i]) {                           # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])              # binomial likelihood
    cloglog(p[i,j]) <- log(Yrs[i]/1) + mu[i] + d[Rx[i,j]] - d[Rx[i,1]]
                                                      # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                  # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                      # deviance contribution
    dummy[i,j]    <- ArmNo[i,j]                       # data not used in this model
    }                                                 # close arm loop
  resdev[i]     <- sum(dev[i,1:NumArms[i]])           # summed deviance contribution
  dummy2[i]     <- RefID[i]                           # data not used in this model
  }                                                   # close study loop
totresdev     <- sum(resdev[])                        # total residual deviance

d[1]<-0                                               # effect is 0 for reference treatment
for (j in 2:NumRx) {                                  # indexes treatments
  d[j] ~ dnorm(0, .0001)                              # vague priors for treatment effects
  }                                                   # close treatment loop

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  cloglog(Tmean[j]) <- log(YrsA) + AMean + d[j]
  cloglog(Tpred[j]) <- log(YrsA) + APred + d[j]
  }

# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                      # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                      # probability that treat j is hth best
    }
  }
}
```

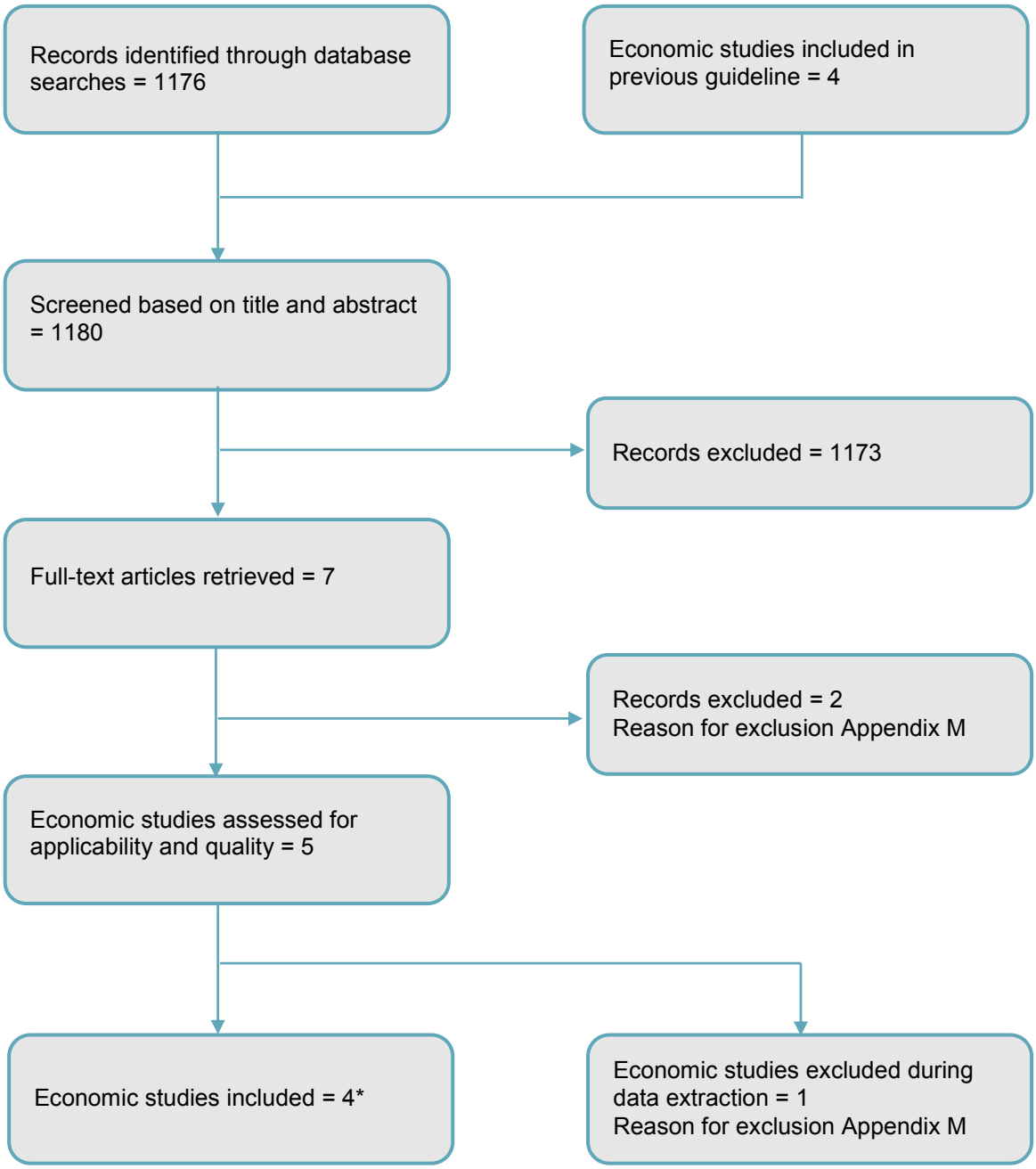
Relative effects withdrawal due to adverse events (random effects)

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
# based on
```

```
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework
# for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                                # indexes studies
  mu[i] ~ dnorm(0, .0001)                               # vague priors for all trial baselines
  delta[i,1] <- 0                                       # effect is zero for control arm
  w[i,1] <- 0                                           # multi-arm adjustment = zero for ctrl
  for (j in 1:NumArms[i]) {                             # indexes arms
    k[i,j]        ~  dbin(p[i,j],N[i,j])              # binomial likelihood
    cloglog(p[i,j]) <- log(Yrs[i] / 1) + mu[i] + delta[i,j] # model for linear predictor
    rhat[i,j]     <- p[i,j] * N[i,j]                  # expected value of the numerators
    dev[i,j]      <- 2 * (k[i,j] * (log(k[i,j])-log(rhat[i,j]))
                     + (N[i,j]-k[i,j]) * (log(N[i,j]-k[i,j]) - log(N[i,j]-rhat[i,j])))
                                                        # deviance contribution
    dummy[i,j]    <- ArmNo[i,j]                         # data not used in this model
    }                                                   # close arm loop
  for (j in 2:NumArms[i]) {                             # indexes arms
    delta[i,j]  ~  dnorm(md[i,j],taud[i,j])           # trial-specific LOR distributions
    md[i,j]     <- d[Rx[i,j]] - d[Rx[i,1]] + sw[i,j] # mean of LOR distributions (with
                                                        # multi-arm trial correction)
    taud[i,j]   <- tau *2*(j-1)/j                     # precision of LOR distributions (with
                                                        # multi-arm trial correction)
    w[i,j]      <- (delta[i,j] - d[Rx[i,j]] + d[Rx[i,1]]) # adjustment for multi-arm RCTs
    sw[i,j]     <- sum(w[i,1:j-1])/(j-1)              # cumulative adjustment for multi-arm
                                                        # trials
    }
  resdev[i]   <- sum(dev[i,1:NumArms[i]])             # summed deviance contribution
  dummy2[i]   <- RefID[i]                             # data not used in this model
  }                                                     # close study loop
totresdev   <- sum(resdev[])                            # total residual deviance

d[1]<-0                                                 # effect is 0 for reference treatment
for (j in 2:NumRx) {                                    # indexes treatments
  d[j] ~ dnorm(0, .0001)                                # vague priors for treatment effects
  }                                                     # close treatment loop
sd  ~  dunif(RFXpriorParam1, RFXpriorParam2)            # uniform between-trial prior
tau <- pow(sd,-2)                                       # between-trial precision

# Provide estimates of treatment effects T[j] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA

AMean ~ dnorm(meanA, precA)
APred ~ dnorm(predA, predPrecA)
for (j in 1:NumRx) {
  cloglog(Tmean[j]) <- log(YrsA) + AMean + d[j]
  cloglog(Tpred[j]) <- log(YrsA) + APred + d[j]
  }

# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(NumRx-1)) {
  for (j in (c+1):NumRx) {
    lHR[c,j]     <- d[j] - d[c]
    log(HR[c,j]) <- lHR[c,j]
    }
  }

# ranking on relative scale
for (j in 1:NumRx) {
  rk[j]       <- blnHiGood*(NumRx+1-rank(d[],j)) + (1-blnHiGood)*rank(d[],j)
  best[j]     <- equals(rk[j],1)                        # probability that treat j is best
  for (h in 1:NumRx) {
    pRk[h,j]  <- equals(rk[j],h)                        # probability that treat j is hth best
    }
  }
```

```
}
```

Appendix J: Economic evidence study selection



*The de novo economic model conducted in the 2013 guideline was reviewed in addition to the studies identified through the search of the published literature.

Appendix K: Economic evidence tables

Study	Buckland 2008			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: cost-utility analysis **Study design:** Decision analytic model **Approach to analysis:** Decision tree starting with either high dose or standard dose mesalazine followed by up to 4 lines of treatment if remission not achieved (outpatient oral steroids, inpatient IV steroids, inpatient IV ciclosporin, surgery) **Perspective:** UK NHS **Time horizon:** 12 weeks **Discounting:** Not applied (<1 year)	**Population:** Adults with mild-to-moderate ulcerative colitis defined by Physician Global Assessment as per ASCEND I/II trials (Hanauer 2005, Hanauer 2007) **INT1:** 2.4g daily mesalazine, **INT2:** 4.8g daily mesalazine	**Total costs (mean per patient):** INT1: £2,474 INT2: £2,382 **Currency & cost year:** GBP (year unclear) **Cost components incorporated:** Drug costs inpatient cost per day, outpatient services and investigations	**QALYs (mean per patient):** INT1: 0.1378 INT2: 0.1394	**Full incremental analysis:** INT2 dominates INT1 **Analysis of uncertainty:** PSA was conducted varying remission rates, health-state utilities and costs. INT2 had the highest probability of being optimal (72%) at a threshold of £30,000/QALY. One-way sensitivity analyses: Utility scores were varied between lower and upper quartiles for EQ5D scores; upper and lower values for all other data were based on 95% CI or by varying data ±25%. Results were sensitive to duration of treatment. INT2 was less costly and also produced -0.0017 QALYs compared to INT1 (ICER<£30,000/QALY).
Data sources				
Health outcomes: Remission rates from Hanauer 2005, Hanauer 2007 **Quality of life weights:** EQ-5D values from Casellas 2005 (Spanish multicentre study) **Costs:** BNF, PSSRU				
Comments				
Source of funding: Procter and Gamble Pharmaceuticals				
Overall applicability: Partially applicable[(a)] **Overall quality**: Potentially serious limitations[(b)]				

(a) Does not include all comparators or sequences of comparators of relevance to the review question
(b) Treatment effects taken from a pooled analysis of 2 trials and may not capture all relevant evidence, does not reflect current practice with respect to rescue therapy, potential conflict of interest

Study	Connolly 2009			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: cost-utility analysis **Study design:** Decision analytic model **Approach to analysis:** Markov model consisting of 5 health states (mesalazine active UC, mesalazine-refractory active UC, steroid-refractory active UC, infliximab active UC; remission) **Perspective:** UK NHS **Time horizon:** 32 weeks (16 weeks in sensitivity analysis) **Discounting:** Not applied (<1 year)	**Population:** People with mild-to-moderate ulcerative colitis (UCDAI score 3-8) based on Marteau 2005 **INT1:** 4g oral mesalazine + placebo enema daily **INT2:** 4g oral mesalazine + 1g/100mL mesalazine enema daily	**Total costs (mean per patient):** INT1: £2,388 INT2: £1,813 **Currency & cost year:** 2008 GBP **Cost components incorporated:** Drug costs , consultations (gastroenterologist, GP), diagnostic tests, blood tests	**QALYs (mean per patient):** INT1: 0.55 INT2: 0.56	**Full incremental analysis:** INT2 dominates INT1 **Analysis of uncertainty:** PSA was conducted varying health state utilities and remission rates for mesalazine as well as for prednisolone and infliximab. Results showed that INT2 had the highest probability of being optimal over threshold values between £0/QALY and £20,000/QALY. A scenario analyses was run with a time horizon of 16 weeks excluding infliximab costs. INT2 dominates INT1.
Data sources				
Health outcomes: Remission rates from Marteau 2005 **Quality of life weights:** EQ-5D from Poole 2008 (PODIUM study) **Costs:** BNF, NHS tariff				
Comments				
Source of funding: Ferring Pharmaceuticals				
Overall applicability: Partially applicable[(a)] **Overall quality**: Potentially serious limitations[(b)]				

(a) Does not include all comparators or sequences of comparators of relevance to the review question
(b) Treatment effects taken from a single study and may not capture all relevant evidence, potential conflict of interest

Study	Brereton 2010			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: cost-utility analysis **Study design:** Decision analytic model **Approach to analysis:** Markov model consisting of 8 health states (active disease with first-line ASA, active disease with increased ASA dose, active disease with second-line treatment, active disease ASA failure, surgery, post-surgery, remission (receiving maintenance treatment) and death) **Perspective:** UK NHS **Time horizon:** 5 years (lifetime horizon in sensitivity analysis) **Discounting:** 3.5% (costs and QALYs)	**Population:** ≥18 yrs mild-to-moderate ulcerative colitis **INT1:** 2.4g daily oral mesalazine, increased to 4.8g if remission not achieved **INT2:** 2.4g daily oral MMX mesalazine increased to 4.8g if remission not achieved	**Total costs (mean per patient):** INT1: £5,574 INT2: £5,582 **Currency & cost year:** GBP (year unclear) **Cost components incorporated:** Drug costs (induction of remission and maintenance), outpatient visits, inpatient stay, surgery	**QALYs (mean per patient):** INT1: 3.434 INT2: 3.445	**Full incremental analysis:** INT2 vs INT1: £749/QALY **Analysis of uncertainty:** PSA was conducted varying health state utilities, costs, odds ratio for remission and probability of surgery. Results showed that INT2 had the highest probability of being optimal (74%) at a threshold of £20,000/QALY. Scenario analyses were run varying: 1. Assumption about adherence to maintenance treatment after achieving induction of remission (INT2 dominates INT1) 2. Time horizon to lifetime including risk of colorectal cancer (INT2 vs. INT1: £7600/QALY)
Data sources				
Health outcomes: Remission rates from Kamm 2007, assumptions about maintenance of remission extrapolated from Kane 2011 **Quality of life weights:** Pooled analysis of two unpublished studies (abstracts by Bassi 2005, Luces 2007) based on EQ-5D/TTO **Costs:** Bassi 2004, NHS tariff				
Comments				
Source of funding: Shire Pharmaceuticals				
Overall applicability: Partially applicable[(a)] **Overall quality**: Very serious limitations[(b)]				

(a) Does not include all comparators or sequences of comparators of relevance to the review question
(b) Treatment effects taken from single study and may not capture all relevant evidence; increased uncertainty due to combined induction of remission model with maintenance of remission extrapolated to 5 years; does not reflect current practice with respect to rescue therapy, potential conflict of interest

Study	Connolly 2014			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: cost-utility analysis **Study design:** Decision analytic model **Approach to analysis:** Markov model consisting of 5 health states (mesalazine active UC, mesalazine-refractory active UC, steroid-refractory active UC, infliximab active UC; remission) **Perspective:** Dutch healthcare system **Time horizon:** 32 weeks **Discounting:** Not applied (<1 year)	**Population:** Mild-to-moderate ulcerative colitis (based on MOTUS trial data by Flourié et al. 2013) **INT1:** 2g oral mesalazine twice daily **INT2:** 4g oral mesalazine once daily	**Total costs (mean per patient):** INT1: £2,978 INT2: £2,600 **Currency & cost year:** 2012 Euros (converted to 2012 GBP) **Cost components incorporated:** Drug costs, consultations (specialist, GP, IBD nurse), follow-up visits, diagnostic tests, other drug treatments	**QALYs (mean per patient):** INT1: 0.56 INT2: 0.57	**Full incremental analysis:** INT2 dominates INT1 **Analysis of uncertainty:** PSA was conducted varying remission rates only; only mean results reported
Data sources				
Health outcomes: Remission rates for mesalazine from Flourié 2013 (MOTUS study) **Quality of life weights:** EQ-5D mapped to disease severity based on UCDAI in Poole et al, 2010 **Costs:** Dutch national tariffs				
Comments				
Source of funding: Ferring International Center				
Overall applicability: Partially applicable[(a)] **Overall quality**: Potentially serious limitations[(b)]				

(a) Does not include all comparators or sequences of comparators of relevance to the review question, non-UK study
(b) Treatment effects taken from single study and may not capture all relevant evidence, full results of PSA not reported, potential conflict of interest

Study	2013 NICE Guideline			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: cost-utility analysis **Study design:** Decision analytic model **Approach to analysis:** Decision tree **Perspective:** UK NHS/PSS **Time horizon:** 28 weeks **Discounting:** Not applied (<1 year)	**Population:** Adults with mild-to-moderate left-sided or extensive ulcerative colitis Comparison of treatment sequences: **INT1:** High-dose oral ASA, add topical ASA, prednisolone **INT2:** High-dose oral ASA, prednisolone **INT3:** Low-dose oral ASA, prednisolone **INT4:** Low-dose oral ASA, add topical ASA, prednisolone **INT5:** Low-dose oral ASA, high oral ASA, prednisolone **INT6:** Low-dose oral ASA, high oral ASA, add topical ASA, prednisolone **INT7:** High-dose oral ASA + topical ASA, prednisolone **INT8:** High-dose oral ASA + beclometasone, prednisolone **INT9:** Low-dose oral ASA, high oral ASA + beclometasone, prednisolone **INT10:** High-dose oral ASA, high oral ASA + beclometasone, prednisolone For all sequences, if remission was not achieved, the model assumed patients progressed to severe ulcerative colitis and were admitted to hospital for inpatient treatment.	**Total costs (mean per patient):** INT1: £1,316 INT2: £2,144 INT3: £2,345 INT4: £1,386 INT5: £1,509 INT6: £1,013 INT7: £1,953 INT8: £1,364 INT9: £1,012 INT10: £984 **Currency & cost year:** 2010 GBP **Cost components incorporated:** Drug costs, consultations (gastroenterologist, GP, IBD nurse, specialist registrar), blood tests, inpatient treatment and surgery	**QALYs (mean per patient):** INT1: 0.468 INT2: 0.463 INT3: 0.458 INT4: 0.465 INT5: 0.459 INT6: 0.461 INT7: 0.472 INT8: 0.481 INT9: 0.469 INT10: 0.472	**Full incremental analysis:** ICER INT8 vs INT10: £42,622/QALY All other strategies are dominated **Analysis of uncertainty:** A number of one-way sensitivity analyses were run varying: 1. utility weights 2. trial durations 3. frequency of GP contact 4. rate of withdrawal from prednisolone 5. efficacy of drugs when not used as first line 6. lower rate of withdrawal from ASA 7. higher rate of withdrawal from ASA Under all sensitivity analyses except #5 INT10 had the highest net monetary benefit PSA was conducted varying treatment effects, utilities and where possible costs. INT10 had the highest probability of being optimal (54%) at a threshold of £20,000/QALY.
Data sources				
Health outcomes: Remission rates and withdrawal rates from systematic review and network meta-analysis of RCTs				

Quality of life weights: EQ-5D mapped to disease severity based on UCDAI in Poole et al, 2010
Costs: NHS Reference costs, PSSRU, drug tariff

Overall applicability: Partially applicable[(a)] **Overall quality**: Minor limitations[(b)]

(a) Does not include all comparators or sequences of comparators of relevance to the review question
(b) Does not reflect current practice with respect to rescue therapy

Appendix L: Health economic analysis

L.1 Introduction

An economic analysis was undertaken in the 2013 Ulcerative colitis guideline to evaluate the cost effectiveness of sequences of pharmacological treatments for the induction of remission of mild-to-moderate left-sided or extensive ulcerative colitis in adults. Since then, new evidence was identified that could affect the 2013 guideline recommendations. This included new randomised controlled trials (RCTs) of treatments that were previously compared in the 2013 cost-effectiveness analysis as well as new RCTs of treatments that were not previously considered.

In addition to the availability of new evidence, the committee wished to revise the approach to the classification of extent of disease and to update some of the assumptions underpinning the cost-effectiveness model in the 2013 guideline to reflect current practice. Therefore, a decision was made to undertake a new cost-effectiveness analysis to compare sequences of pharmacological treatments for the induction of remission of mild-to-moderate ulcerative colitis drawing on the data from RCTs identified in the clinical evidence review and synthesised using network meta-analysis as described in Appendix I.

L.2 Methods

L.2.1 Overview

A cost–utility analysis was constructed from a UK NHS/personal social services perspective with costs reported in GBP (£) and health outcomes reported as quality-adjusted life years (QALYs).

L.2.2 Population

The cost-effectiveness model in the 2013 guideline considered adults with mild-to-moderate left-sided or extensive ulcerative colitis, defined as greater than 30–40cm from the anal verge. The committee agreed that a revised approach to classification of extent of disease should be adopted based on the following definitions:

- proctitis: <15cm
- proctosigmoiditis and left-sided: 15–50cm
- extensive: >50cm.

The new cost-effectiveness model compares different treatment sequences in adults (18 years and older) for each of the 3 sub-populations listed above. There was insufficient evidence to inform a comparative cost-effectiveness analysis of treatment sequences for any extent of disease in young people and children. Dosing for some of the drugs of interest to the anlaysis differs between adults and children and therefore it was not considered appropriate to do a combined cost-effectiveness analysis.

L.2.3 Comparators

Treatment sequences for the cost-effectiveness model were defined by taking into consideration:

- the approach to the economic analysis described in the 2013 guideline
- the available clinical evidence for different treatments in each extent of disease
- the committee's experience of current clinical practice and areas of uncertainty where modelling specific treatment sequences could help inform clinical practice.

An initial list of clinically plausible treatment sequences was generated based on the following guidance from the committee:

- Aminosalicylates are generally used as first-line treatment in all extents of disease and can be given as oral preparations, topical preparations or a combination of both. The use of oral corticosteroids is generally reserved for later lines of treatment because of cocnerns about side effects. Topical corticosteroids are less commonly used than topical aminosalicylates; however, the committee was unaware of an evidence base for this practice, and agreed that there are circumstances under which it could be reasonable to treat a new episode of active disease with first-line topical corticosteroids (for example, if a person has a history of response to or preference for topical corticosteroids). Therefore, the committee agreed it would be useful to simulate sequences starting with topical corticosteroids in the model for proctosigmoiditis and left-sided disease.
- For people whose disease does not respond to initial treatment with a topical aminosalicylate, it is common to add an oral aminosalicylate.
- For people whose disease does not respond to initial treatment with an oral aminosalicylate, options include: 1) increasing the dose (if not already on high dose) 2) adding a topical aminosalicylate preparation 3) adding a corticosteroid.
- If a person withdraws from treatment with an oral aminosalicylate due to side effects, options include: 1) lowering the dose (if not already on low dose) 2) trying a different aminosalicylate.
- Sequences should not include more than 1 line of oral corticosteroid treatment before considering rescue therapy.
- Although placebo was a common comparator in RCTs, the committee did not feel that 'no treatment' would be a clinically relevant comparator in the economic model. The analysis does not distinguish between people who are presenting with ulcerative colitis for the first time and those who are experiencing an inflammatory exacerbation. Some people may be receiving maintenance treatment such as an oral aminosalicylate prior to experiencing an inflammatory exacerbation and the committee advised that in clinical practice, people would likely continue this as the backbone of long-term treatment. In addition, the objective of this analysis was to compare different sequences of treatments to induce remission. The analysis did not consider different strategies with respect to the optimal timing of initiating treatment, for example no treatment initially followed by treatment at a later point in time or initial treatment followed by no treatment in people whose disease was still active.

The majority (>80%) of RCTs of oral aminosalicylates that were included in the clinical evidence review were of mesalazine preparations. The committee agreed that mesalazine should be the preferred or default aminosalicylate in the cost-effectiveness model but that olsalazine or balsalzide could be considered if a person withdraws from mesalazine treatment due to side effects. In adults, sulfasalazine would generally not be used unless the person also had inflammatory joint disease.

The committee noted that, in current clinical practice, when oral and topical corticosteroids are used for induction of remission of mild-to-moderate ulcerative colitis, they are generally added to oral aminosalicylate treatment. However, in many RCTs, concomitant treatments were not consistently reported. In the cost-effectiveness model, it was assumed that:

- In line with its licensed indication, oral beclometasone would only be used as adjunct treatment to aminosalicylates

- Other oral corticosteroids (budesonide, prednisolone) and topical corticosteroids (budesonide, prednisolone and hydrocortisone) would also be used in addition to a low-dose oral aminosalicylate unless a person had withdrawn from oral aminosalicylate treatment earlier in the sequence, in which case these drugs would be used alone.

These principles only applied in calculating the costs of treatment; it was assumed that the effect of concomitant aminosalicylate therapy would be captured in the RCT evidence.

Treatment sequences contained up to 4 lines of treatment in proctitis and up to 3 lines of treatment in other extents of disease. In the model, if a person's disease had not entered remission after 3 or 4 lines of treatment, it was assumed that their disease had progressed to severe ulcerative colitis and that they would receive further treatment as described in the 2013 guideline and NICE technologicy appraisals Infliximab for acute exacerbations of ulcerative colitis (TA163), Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329) and Vedolizumab for treating moderately to severely active ulcerative colitis (TA342). This included IV hydrocortisone as a first step, followed by IV ciclosporin, biological therapy or surgery.

L.2.4 Structure

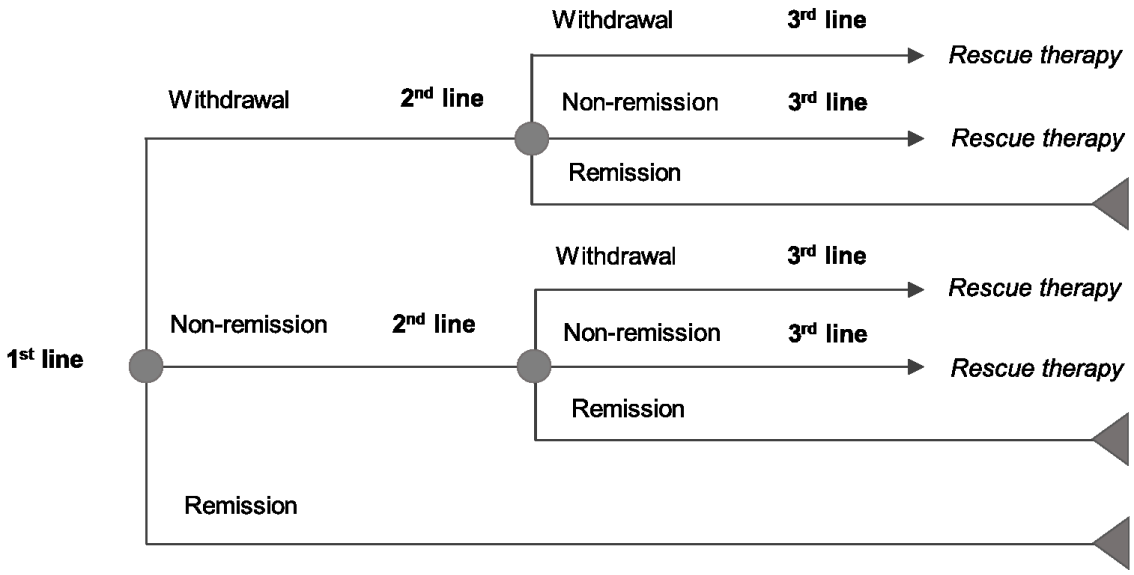
None of the RCTs included in the evidence review compared sequences of treatments or more than 1 line of treatment for the induction of remission of mild-to-moderate ulcerative colitis. In order to model the cost effectiveness of different treatment sequences, the committee discussed and agreed it was necessary to make a number of key assumptions about the model structure, including:

- The probability of a person's disease entering remission is independent of the line of treatment in which a drug is used.
- Once a person's disease enters remission, it is assumed to remain in remission for the duration of the model.

The cost-effectiveness model was constructed as a decision tree. For each line of treatment, there are three possible mutually exclusive outcomes:

- Withdrawal from treatment due to adverse events; switch to next line of treatment
- Non-remission; switch to next line of treatment
- Remission.

Figure 36: Structure of the decision tree for a single sequence of treatments



The time-point at which clinical remission was reported varied across the RCTs that were included in the clinical review. To inform assumptions about treatment duration in the cost-effectiveness model, the length of follow-up across RCTs was summarised for each drug and presented to the committee to discuss their relevance to current UK clinical practice. In most cases, the most frequently reported time point for remission that was reported in RCTs was aligned with the duration of treatment in clinical practice except for the following:

- Only 1 study (Lennard Jones 1960) provided information on remission rates for oral prednisolone in extensive disease; in this study, clinical remission was reported at 4 weeks but the committee agreed this did not reflect current practice and that an 8-week tapering course should be assumed in the model
- Studies of topical budesonide and topical hydrocortisone ranged from 5 to 8 weeks with the most frequently reported timepoint at 6 weeks, but the committee agreed that the model should assume a 4-week duration for all topical corticosteroids.
- Only 1 study (Vecchi 2001) reported remission rates for low-dose oral mesalazine in combination with topical mesalazine at 6 weeks in people with proctosigmoiditis and left-sided disease; the committee agreed that, in clinical practice, the combination was likely to be given for 8 weeks, which was in line with the duration of treatment for high-dose oral mesalazine in combination with topical mesalazine in extensive disease.

In discussing duration of treatment, the committee noted that, for all drugs, response to treatment would generally be assessed earlier than the follow-up durations reported across RCTs so that, in the event of non-response, a decision could be made whether to switch to another drug. It was therefore necessary to make the following additional assumptions:

- According to the committee, response to treatment would generally be assessed halfway through a full course of treatment for the induction of remission, at which point people whose disease is not responding to treatment would move to the next line of treatment in the sequence. In the model, for any given line of treatment, it was assumed that the duration of treatment for people in the non-remission branch of the decision tree was half that of people in the remission branch. This assumption is a departure from the approach adopted in the 2013 model, in which people who did not withdraw owing to adverse

events were all assumed to undergo treatment of the same duration, regardless of response. The assumption we have adopted for this update has the advantage of reflecting real-world practice, in which people whose disease shows no response to treatment would be very unlikely to complete a full course of equal duration to people whose condition is improving. It has the disadvantage that we are effectively assuming that remission status can be accurately known partway through a full course of treatment. A superior approach would be to model final clinical remission conditional on initial response as a separate outcome; however, while some RCTs report 'clinical response' (or a similar outcome that might be usable for this purpose), there were insufficient data reported across the range of treatments and extents of disease needed to make this approach feasible. Similarly, very few RCTs reported remission at multiple timepoints. Given the potential importance of these assumptions, we configured the model to be able to adopt the assumption of equal duration of treatment for remission and non-remission – as per the 2013 model – and tested the impact in sensitivity analysis for all extents of disease.

- In common with the 2013 model, the new analysis also assumes that people in the remission branch would begin to experience improvements in health status associated with their disease entering remission halfway through a full course of treatment.
- As adverse events are, on average, likely to emerge relatively early in treatment, the duration of treatment for people in the withdrawal branch of the decision tree was assumed to be half of that of people in the non-remission branch.
- The model allows for the next line of treatment in a sequence to differ following withdrawal versus non-remission. This flexibility, which represents a departure from the 2013 modelling, is critical to prevent illogical sequences. For example, people discontinuing a low-dose aminosalicylate owing to toxicity would not move to a high dose of the same agent, whereas this is an entirely rational strategy if the switch is made because the person's disease has not responded to low-dose therapy.

Table 50: Treatment sequences for proctitis

Strategy	1st line	Following non-remission			Following withdrawal		
		2nd line	3rd line	4th line	2nd line	3rd line	4th line
PRC1 – PRC4: Start with topical ASA, add low-dose oral ASA, keep low-dose oral ASA and add topical or oral corticosteroid, topical tacrolimus							
PRC1	tASA	LD oASA + tASA	LD oASA + tCS (pred)	tTAC	LD oASA	tCS (pred)	tTAC
PRC2	tASA	LD oASA + tASA	LD oASA + oCS (pred)	tTAC	LD oASA	oCS (pred)	tTAC
PRC3	tASA	LD oASA + tASA	LD oASA + oCS (beclo)	tTAC	LD oASA	oCS (pred)	tTAC
PRC4	tASA	LD oASA + tASA	LD oASA + oCS (bude)	tTAC	LD oASA	oCS (bude)	tTAC
PRC5 – PRC8: Start with low-dose oral ASA, add topical ASA, keep low-dose oral ASA and add topical or oral corticosteroid, topical tacrolimus							
PRC5	LD oASA	LD oASA + tASA	LD oASA + tCS (pred)	tTAC	tASA	tCS (pred)	tTAC
PRC6	LD oASA	LD oASA + tASA	LD oASA + oCS (pred)	tTAC	tASA	oCS (pred)	tTAC
PRC7	LD oASA	LD oASA + tASA	LD oASA + oCS (beclo)	tTAC	tASA	oCS (pred)	tTAC
PRC8	LD oASA	LD oASA + tASA	LD oASA + oCS (bude)	tTAC	tASA	oCS (bude)	tTAC
PRC9 – PRC16: Start with combination low-dose oral and topical ASA, keep low-dose oral ASA and add topical or oral corticosteroid, topical tacrolimus							
PRC9	LD oASA + tASA	LD oASA + tCS (pred)	tTAC	-	tASA	tCS (pred)	tTAC
PRC10	LD oASA + tASA	LD oASA + oCS (pred)	tTAC	-	tASA	oCS (pred)	tTAC
PRC11	LD oASA + tASA	LD oASA + oCS (beclo)	tTAC	-	tASA	oCS (pred)	tTAC
PRC12	LD oASA + tASA	LD oASA + oCS (bude)	tTAC	-	tASA	oCS (bude)	tTAC
PRC13	LD oASA + tASA	LD oASA + tCS (pred)	tTAC	-	LD oASA	tCS (pred)	tTAC
PRC14	LD oASA + tASA	LD oASA + oCS (pred)	tTAC	-	LD oASA	oCS (pred)	tTAC
PRC15	LD oASA + tASA	LD oASA + oCS (beclo)	tTAC	-	LD oASA	oCS (pred)	tTAC
PRC16	LD oASA + tASA	LD oASA + oCS (bude)	tTAC	-	LD oASA	oCS (bude)	tTAC
PRC17 – PRC20: Start with topical ASA, add low-dose oral ASA, keep low-dose oral ASA and add topical or oral corticosteroid							
PRC17	tASA	LD oASA + tASA	LD oASA + tCS (pred)	-	LD oASA	tCS (pred)	-
PRC18	tASA	LD oASA + tASA	LD oASA + oCS (pred)	-	LD oASA	oCS (pred)	-
PRC19	tASA	LD oASA + tASA	LD oASA + oCS (beclo)	-	LD oASA	oCS (pred)	-

Strategy	1st line	Following non-remission			Following withdrawal		
		2nd line	3rd line	4th line	2nd line	3rd line	4th line
PRC20	tASA	LD oASA + tASA	LD oASA + oCS (bude)	-	LD oASA	oCS (bude)	-
PRC21 – PRC24: Start with low-dose oral ASA, add topical ASA, keep low-dose oral ASA and add topical or oral corticosteroid							
PRC21	LD oASA	LD oASA + tASA	LD oASA + tCS (pred)	-	tASA	tCS (pred)	-
PRC22	LD oASA	LD oASA + tASA	LD oASA + oCS (pred)	-	tASA	oCS (pred)	-
PRC23	LD oASA	LD oASA + tASA	LD oASA + oCS (beclo)	-	tASA	oCS (pred)	-
PRC24	LD oASA	LD oASA + tASA	LD oASA + oCS (bude)	-	tASA	oCS (bude)	-
PRC25 – PRC32: Start with combination low-dose oral and topical ASA, keep low-dose oral ASA and add topical or oral corticosteroid							
PRC25	LD oASA + tASA	LD oASA + tCS (pred)	-	-	tASA	tCS (pred)	-
PRC26	LD oASA + tASA	LD oASA + oCS (pred)	-	-	tASA	oCS (pred)	-
PRC27	LD oASA + tASA	LD oASA + oCS (beclo)	-	-	tASA	oCS (pred)	-
PRC28	LD oASA + tASA	LD oASA + oCS (bude)	-	-	tASA	oCS (bude)	-
PRC29	LD oASA + tASA	LD oASA + tCS (pred)	-	-	LD oASA	tCS (pred)	-
PRC30	LD oASA + tASA	LD oASA + oCS (pred)	-	-	LD oASA	oCS (pred)	-
PRC31	LD oASA + tASA	LD oASA + oCS (beclo)	-	-	LD oASA	oCS (pred)	-
PRC32	LD oASA + tASA	LD oASA + oCS (bude)	-	-	LD oASA	oCS (bude)	-

PRC = proctitis; LD = low-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; tTAC = topical tacrolimus

Table 51: Treatment sequences for proctosigmoiditis and left-sided disease

Strategy	1st line	Following non-remission		Following withdrawal	
		2nd line	3rd line	2nd line	3rd line
PLS1 – PLS12: Start with low-dose oral ASA, increase to high-dose oral ASA, keep low-dose oral ASA and add oral or topical corticosteroid					
PLS1	LD oASA	HD oASA	LD oASA + oCS (pred)	HD oASA (olsalazine)	oCS (pred)
PLS2	LD oASA	HD oASA	LD oASA + oCS (beclo)	HD oASA (olsalazine)	oCS (pred)
PLS3	LD oASA	HD oASA	LD oASA + oCS (bude)	HD oASA (olsalazine)	oCS (bude)
PLS4	LD oASA	HD oASA	LD oASA + oCS (pred)	HD oASA (balsalazide)	oCS (pred)
PLS5	LD oASA	HD oASA	LD oASA + oCS (beclo)	HD oASA (balsalazide)	oCS (pred)
PLS6	LD oASA	HD oASA	LD oASA + oCS (bude)	HD oASA (balsalazide)	oCS (bude)
PLS7	LD oASA	HD oASA	LD oASA + tCS (pred)	HD oASA (olsalazine)	tCS (pred)
PLS8	LD oASA	HD oASA	LD oASA + tCS (hydro)	HD oASA (olsalazine)	tCS (hydro)
PLS9	LD oASA	HD oASA	LD oASA + tCS (bude)	HD oASA (olsalazine)	tCS (bude)
PLS10	LD oASA	HD oASA	LD oASA + tCS (pred)	HD oASA (balsalazide)	tCS (pred)
PLS11	LD oASA	HD oASA	LD oASA + tCS (hydro)	HD oASA (balsalazide)	tCS (hydro)
PLS12	LD oASA	HD oASA	LD oASA + tCS (bude)	HD oASA (balsalazide)	tCS (bude)
PLS13 – PLS24: Start with low-dose oral ASA, add topical ASA, keep low-dose oral ASA and add oral or topical corticosteroid					
PLS13	LD oASA	LD oASA + tASA	LD oASA + oCS (pred)	HD oASA (olsalazine)	oCS (pred)
PLS14	LD oASA	LD oASA + tASA	LD oASA + oCS (beclo)	HD oASA (olsalazine)	oCS (pred)
PLS15	LD oASA	LD oASA + tASA	LD oASA + oCS (bude)	HD oASA (olsalazine)	oCS (bude)
PLS16	LD oASA	LD oASA + tASA	LD oASA + oCS (pred)	HD oASA (balsalazide)	oCS (pred)
PLS17	LD oASA	LD oASA + tASA	LD oASA + oCS (beclo)	HD oASA (balsalazide)	oCS (pred)
PLS18	LD oASA	LD oASA + tASA	LD oASA + oCS (bude)	HD oASA (balsalazide)	oCS (bude)
PLS19	LD oASA	LD oASA + tASA	LD oASA + tCS (pred)	HD oASA (olsalazine)	tCS (pred)
PLS20	LD oASA	LD oASA + tASA	LD oASA + tCS (hydro)	HD oASA (olsalazine)	tCS (hydro)
PLS21	LD oASA	LD oASA + tASA	LD oASA + tCS (bude)	HD oASA (olsalazine)	tCS (bude)
PLS22	LD oASA	LD oASA + tASA	LD oASA + tCS (pred)	HD oASA (balsalazide)	tCS (pred)
PLS23	LD oASA	LD oASA + tASA	LD oASA + tCS (hydro)	HD oASA (balsalazide)	tCS (hydro)

Strategy	1st line	Following non-remission		Following withdrawal	
		2nd line	3rd line	2nd line	3rd line
PLS24	LD oASA	LD oASA + tASA	LD oASA + tCS (bude)	HD oASA (balsalazide)	tCS (bude)
PLS25 – PLS30: Start with high-dose oral ASA, add topical ASA, keep low-dose oral ASA and add oral or topical corticosteroid					
PLS25	HD oASA	LD oASA + tASA	LD oASA + oCS (pred)	LD oASA	oCS (pred)
PLS26	HD oASA	LD oASA + tASA	LD oASA + oCS (beclo)	LD oASA	oCS (pred)
PLS27	HD oASA	LD oASA + tASA	LD oASA + oCS (bude)	LD oASA	oCS (bude)
PLS28	HD oASA	LD oASA + tASA	LD oASA + tCS (pred)	LD oASA	tCS (pred)
PLS29	HD oASA	LD oASA + tASA	LD oASA + tCS (hydro)	LD oASA	tCS (hydro)
PLS30	HD oASA	LD oASA + tASA	LD oASA + tCS (bude)	LD oASA	tCS (bude)
PLS31 – PLS36: Start with topical ASA, add low-dose oral ASA, keep low-dose oral ASA and add oral or topical corticosteroid					
PLS31	tASA	LD oASA + tASA	LD oASA + oCS (pred)	LD oASA	oCS (pred)
PLS32	tASA	LD oASA + tASA	LD oASA + oCS (beclo)	LD oASA	oCS (pred)
PLS33	tASA	LD oASA + tASA	LD oASA + oCS (bude)	LD oASA	oCS (bude)
PLS34	tASA	LD oASA + tASA	LD oASA + tCS (pred)	LD oASA	tCS (pred)
PLS35	tASA	LD oASA + tASA	LD oASA + tCS (hydro)	LD oASA	tCS (hydro)
PLS36	tASA	LD oASA + tASA	LD oASA + tCS (bude)	LD oASA	tCS (bude)
PLS37 – PLS48: Start with combination low-dose oral and topical ASA, keep low-dose oral ASA and add oral or topical corticosteroid					
PLS37	LD oASA + tASA	LD oASA + oCS (pred)	-	LD oASA	oCS (pred)
PLS38	LD oASA + tASA	LD oASA + oCS (beclo)	-	LD oASA	oCS (pred)
PLS39	LD oASA + tASA	LD oASA + oCS (bude)	-	LD oASA	oCS (bude)
PLS40	LD oASA + tASA	LD oASA + tCS (pred)	-	LD oASA	tCS (pred)
PLS41	LD oASA + tASA	LD oASA + tCS (hydro)	-	LD oASA	tCS (hydro)
PLS42	LD oASA + tASA	LD oASA + tCS (bude)	-	LD oASA	tCS (bude)
PLS43	LD oASA + tASA	LD oASA + oCS (pred)	-	tASA	oCS (pred)
PLS44	LD oASA + tASA	LD oASA + oCS (beclo)	-	tASA	oCS (pred)
PLS45	LD oASA + tASA	LD oASA + oCS (bude)	-	tASA	oCS (bude)
PLS46	LD oASA + tASA	LD oASA + tCS (pred)	-	tASA	tCS (pred)

Strategy	1st line	Following non-remission		Following withdrawal	
		2nd line	3rd line	2nd line	3rd line
PLS47	LD oASA + tASA	LD oASA + tCS (hydro)	-	tASA	tCS (hydro)
PLS48	LD oASA + tASA	LD oASA + tCS (bude)	-	tASA	tCS (bude)
PLS49 – PLS57: Start with topical corticosteroid, switch to low-dose oral ASA, keep low-dose oral ASA and add oral corticosteroid					
PLS49	tCS (hydro)	LD oASA	LD oASA + oCS (pred)	LD oASA	oCS (pred)
PLS50	tCS (hydro)	LD oASA	LD oASA + oCS (beclo)	LD oASA	oCS (pred)
PLS51	tCS (hydro)	LD oASA	LD oASA + oCS (bude)	LD oASA	oCS (bude)
PLS52	tCS (bude)	LD oASA	LD oASA + oCS (pred)	LD oASA	oCS (pred)
PLS53	tCS (bude)	LD oASA	LD oASA + oCS (beclo)	LD oASA	oCS (pred)
PLS54	tCS (bude)	LD oASA	LD oASA + oCS (bude)	LD oASA	oCS (bude)
PLS55	tCS (pred)	LD oASA	LD oASA + oCS (pred)	LD oASA	oCS (pred)
PLS56	tCS (pred)	LD oASA	LD oASA + oCS (beclo)	LD oASA	oCS (pred)
PLS57	tCS (pred)	LD oASA	LD oASA + oCS (bude)	LD oASA	oCS (bude)
PLS58 – PLS66: Start with topical corticosteroid, switch to high-dose oral ASA, keep low-dose oral ASA and add oral corticosteroid					
PLS58	tCS (hydro)	HD oASA	LD oASA + oCS (pred)	HD oASA	oCS (pred)
PLS59	tCS (hydro)	HD oASA	LD oASA + oCS (beclo)	HD oASA	oCS (pred)
PLS60	tCS (hydro)	HD oASA	LD oASA + oCS (bude)	HD oASA	oCS (bude)
PLS61	tCS (bude)	HD oASA	LD oASA + oCS (pred)	HD oASA	oCS (pred)
PLS62	tCS (bude)	HD oASA	LD oASA + oCS (beclo)	HD oASA	oCS (pred)
PLS63	tCS (bude)	HD oASA	LD oASA + oCS (bude)	HD oASA	oCS (bude)
PLS64	tCS (pred)	HD oASA	LD oASA + oCS (pred)	HD oASA	oCS (pred)
PLS65	tCS (pred)	HD oASA	LD oASA + oCS (beclo)	HD oASA	oCS (pred)
PLS66	tCS (pred)	HD oASA	LD oASA + oCS (bude)	HD oASA	oCS (bude)
PLS67 – PLS75: Start with topical corticosteroid, switch to combination low-dose oral and topical ASA, keep low-dose oral ASA and add oral corticosteroid					
PLS67	tCS (hydro)	LD oASA + tASA	LD oASA + oCS (pred)	LD oASA + tASA	oCS (pred)
PLS68	tCS (hydro)	LD oASA + tASA	LD oASA + oCS (beclo)	LD oASA + tASA	oCS (pred)

Strategy	1st line	Following non-remission		Following withdrawal	
		2nd line	3rd line	2nd line	3rd line
PLS69	tCS (hydro)	LD oASA + tASA	LD oASA + oCS (bude)	LD oASA + tASA	oCS (bude)
PLS70	tCS (bude)	LD oASA + tASA	LD oASA + oCS (pred)	LD oASA + tASA	oCS (pred)
PLS71	tCS (bude)	LD oASA + tASA	LD oASA + oCS (beclo)	LD oASA + tASA	oCS (pred)
PLS72	tCS (bude)	LD oASA + tASA	LD oASA + oCS (bude)	LD oASA + tASA	oCS (bude)
PLS73	tCS (pred)	LD oASA + tASA	LD oASA + oCS (pred)	LD oASA + tASA	oCS (pred)
PLS74	tCS (pred)	LD oASA + tASA	LD oASA + oCS (beclo)	LD oASA + tASA	oCS (pred)
PLS75	tCS (pred)	LD oASA + tASA	LD oASA + oCS (bude)	LD oASA + tASA	oCS (bude)

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; hydro = hydrocortisone

Table 52: Treatment sequences for extensive disease

Strategy	1st line	Following non-remission		Following withdrawal	
		2nd line	3rd line	2nd line	3rd line
EXT1 – EXT3: Start with high-dose oral ASA, add topical ASA, keep low-dose oral ASA and add oral corticosteroid					
EXT1	HD oASA	HD oASA + tASA	LD oASA + oCS (bude)	LD oASA	oCS (bude)
EXT2	HD oASA	HD oASA + tASA	LD oASA + oCS (beclo)	LD oASA	oCS (pred)
EXT3	HD oASA	HD oASA + tASA	LD oASA + oCS (pred)	LD oASA	oCS (pred)
EXT4 – EXT6: Start with combination high-dose oral and topical ASA, keep low-dose oral ASA and add oral corticosteroid					
EXT4	HD oASA + tASA	LD oASA + oCS (bude)	-	LD oASA	-
EXT5	HD oASA + tASA	LD oASA + oCS (beclo)	-	LD oASA	-
EXT6	HD oASA + tASA	LD oASA + oCS (pred)	-	LD oASA	-

EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; hydro = hydrocortisone

The base-case assumptions about the duration of treatment for each drug in the event of remission, non-remission and withdrawal are summarised in Table 53 and were applied in all extents of disease. Given these assumptions, the length of the longest treatment sequence (including rescue therapy) was 30 weeks and this was adopted as the time horizon for the cost-effectiveness model. No discounting was applied to either costs or health outcomes as the time horizon was less than 1 year.

Table 53: Treatment duration assumptions in the base-case cost-effectiveness analyses

Treatment	Duration of follow-up in RCTs (weeks)	Treatment duration assumed in model (base case)		
		Remission	Non-remission	Withdrawal
LD oASA	4-8	8	4	2
LD oASA + tASA	6	8	4	2
HD oASA	8-10	8	4	2
HD oASA + tASA	8	8	4	2
tASA	2-6	4	2	1
oCS (pred) ± LD oASA	4	8	4	2
oCS (beclo) + LD oASA	4	4	2	1
oCS (bude) ± LD oASA	8	8	4	2
tCS (pred) ± LD oASA	2-4	4	2	1
tCS (bude) ± LD oASA[(a)]	6-8	4	2	1
tCS (hydro) ± LD oASA[(a)]	5-8	4	2	1
Topical tacrolimus	8	8	4	2

LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; hydro = hydrocortisone

(a) Omitted from base-case analysis in proctosigmoiditis and left-sided disease because treatment duration in RCTs exceeded committee assumption about treatment duration in clinical practice

For some drugs, there was a discrepancy between the duration of follow-up reported in RCTs and the assumption about duration of treatment for achieving remission in clinical practice. In the base-case cost-effectiveness analyses, a conservative approach was adopted and drugs were only included if the RCT evidence reported remission at a timepoint that was equal to or less than the assumption about the duration of treatment in clinical practice. For example, the duration of treatment for oral prednisolone was assumed to be 8 weeks while RCT evidence reported remission at 4 weeks and therefore sequences containing oral prednisolone were permitted. However, for topical budesonide and topical hydrocortisone, treatment duration was assumed to be 4 weeks in clinical practice while RCT evidence of remission was only available at 5-8 weeks and therefore sequences containing these drugs were not modelled in the base case. A sensitivity analysis was run in which the duration of treatment was set to the maximum follow-up reported for each drug across all RCTs, allowing for additional sequences with topical budesonide and topical hydrocortisone to be modelled in proctosigmoiditis and left-sided disease.

L.2.5 Model parameters

L.2.5.1 General approach

With the exception of remission and withdrawal rates, which were based on the systematic review and network meta-analyses reported in Appendix I, parameter inputs were identified by reviewing the economic model in the 2013 guideline and by undertaking informal searches to identify additional sources of information that may have been published since then. The aim of the informal searches was to satisfy the principle of saturation (Kaltenthaler 2011). Searches were conducted in a variety of general databases, including Medline (via PubMed), Google Scholar and the CEA (Cost-Effectiveness Analysis) Registry. As part of the systematic review of published cost-effectiveness evaluations, articles that did not meet formal inclusion criteria but appeared to be relevant to the decision problem were retrieved and the reference lists of these articles were scanned to identify further sources of inputs for the model.

L.2.5.2 Clinical outcomes

Baseline estimates for remission and withdrawals due to adverse events

The baseline estimates of remission and withdrawals due to adverse events were informed by the reference treatment arms of RCTs in each of the evidence networks described in Appendix I. Alternative sources for estimating baseline events were considered, as recommended in NICE DSU TSD5. However, while the epidemiological literature provides some insight into the clinical course of ulcerative colitis with respect to duration of remission and risk of relapse over time, the outcomes of interest to the cost-effectiveness analysis (induction of remission and withdrawal due to adverse events) are more readily characterised within the context of RCTs.

Low-dose oral aminosalicylate was chosen as the reference treatment because it was the only active treatment that was present in all networks across all time points and extents of disease, with the exception of extensive disease at 5-8 weeks where it was necessary to use high-dose oral aminosalicylate as the reference treatment. Only 1 arm was available to inform the baseline probability of remission in proctitis at 0-4 weeks (Gionchetti 1998) and at 5-8 weeks (Ito 2010). In all other cases, all available reference treatment arms were included in the pooled estimates presented in Table 54 (see L.5 for WinBUGS code used for synthesis).

Table 54: Baseline log-rate for withdrawal and log-odds of remission

Reference treatment	Network	ln(rate) (SE)
LD oASA	Withdrawal all extents and time points	-0.806 (0.104)
Reference treatment	**Network**	**ln(odds) (SE)**
LD oASA	Remission proctitis (0-4 weeks)	-0.348 (0.377)
LD oASA	Remission proctitis (5-8 weeks)	-0.635 (0.151)
LD oASA	Remission proctosigmoiditis and left-sided (0-4 weeks)	-1.169 (0.100)
LD oASA	Remission proctosigmoiditis and left-sided (5-8 weeks)	-0.592 (0.057)
LD oASA	Remission extensive (0-4 weeks)	-0.220 (0.325)
HD oASA	Remission extensive (5-8 weeks)	-0.019 (0.208)

Due to the sparseness of the evidence networks in proctitis, the baseline odds of remission for low-dose oral aminosalicylates at both 0–4 weeks and 5–8 weeks were estimated on the basis of only one study each. This produced a higher point estimate for the probability of

remission at 0–4 weeks (0.414, 95% CI 0.244 to 0.594) than at 5–8 weeks (0.346, 95% CI 0.283 to 0.416). This finding appears at odds with our assumption (and the committee's expectation) that more people achieve remission as time goes on; however, the substantially overlapping confidence intervals suggest that the result may be explained by simple sampling error. Nevertheless, although the cost-effectiveness model does not rely on direct comparisons of baseline events between timepoints, in order to improve coherence of model inputs, an additional constraint was applied in probabilistic sensitivity analysis that required the baseline probability of remission at 5–8 weeks to be equal to or greater than the baseline probability of remission at 0–4 weeks.

Relative treatment effects for remission

Where there was information on remission rates for more than 1 drug of the same class at the same timepoint in the same extent of disease, different models were tested to determine if there was any statistical benefit to accounting for heterogeneity at the individual drug level, by mode of administration and by dose (Appendix B and I). In proctosigmoiditis and left-sided disease, where the largest number of studies was identified, no statistical differences between topical aminosalicylate preparations were found and therefore remission rates were modelled at the class level. Oral aminosalicylates were divided into low-dose and high-dose regimens (used alone or in combination) and analysed at the class level. These class-level effects for aminosalicylates were assumed to also apply to other timepoints and other extents of disease.

To maximise the amount of data informing the economic model, estimates of relative effects were based on the results of the relevant network meta-analyses for 0-4 weeks and 5-8 weeks in each extent of disease. Given the available evidence, it was not possible to directly establish whether a class-level effect could also be applied to corticosteroids, because the individual drugs within the class were not all connected in a common network. For topical corticosteroids, information on remission rates was available for prednisolone at 0–4 weeks and for budesonide and hydrocortisone at 5–8 weeks in proctosigmoiditis and left-sided disease. For oral corticosteroids, information on remission rates was available for beclomestasone at 0–4 weeks and budesonide at 5–8 weeks in proctosigmoiditis and left-sided disease and for prednisolone at 0–4 weeks in extensive disease. Therefore, in the cost-effectiveness analyses it was necessary to model remission rates for topical and oral corticosteroids at the level of the individual drugs.

In several cases, there was no information available from RCTs to estimate remission rates for a given drug in a specific extent of disease at a specific time point where the committee was interested in including that drug as part of a treatment sequence. This was particularly relevant in the following cases:

- There was only 1 study (Lennard Jones 1960) in the evidence review that provided data on remission rates for oral prednisolone. This study was a comparison of oral prednisolone and low-dose sulfasalazine in extensive disease and reported remission rates at 4 weeks. Given the role of oral prednisolone in clinical practice, the committee felt it was important to model sequences containing predinsolone in all extents of disease.
- In proctitis, the evidence review did not identify any studies of topical corticosteroids, oral corticosteroids or combination treatment with an oral and topical aminosalicylate, but the committee felt all of these would be relevant options.

To address these gaps, we configured the cost-effectiveness model to be able to borrow information on relative effectiveness from elsewhere in the evidence base according to the following hierarchy:

- from an earlier timepoint in the same extent of disease or, failing that,
- from the same timepoint in a greater extent of disease or, failing that,

- from an earlier timepoint in a greater extent of disease.

This was considered to be a conservative approach because it was assumed that, all other things equal, the relative effectiveness of a drug could be expected to be the same or lower at an earlier timepoint in a greater extent of disease.

Relative treatment effects for withdrawal

Not all RCTs identified in the evidence review reported withdrawal rates due to adverse events. There were insufficient data to inform withdrawal rates by extent of disease for all drugs. Therefore, it was necessary to combine withdrawal data from all studies into a single network that was used to inform the cost-effectiveness analyses for all extents of disease. The committee agreed that this was a reasonable approach, based on their experience that extent of disease has much less influence on tolerability than on effectiveness.

No studies reported information on withdrawal due to adverse events for oral prednisolone, topical prednisolone, topical hydrocortisone or topical tacrolimus. Where possible, assumptions about withdrawal due to adverse events were borrowed from another drug of the same class and mode of administration. For example, an assumption was made that oral prednisolone would have the same rate of withdrawal as oral budesonide, which reported the highest point-estimate for withdrawal out of the oral corticosteroids in the network meta-analysis (Appendix I). Topical prednisolone and topical hydrocortisone were assigned the same withdrawal rate as topical budesonide. However, as topical tacrolimus was the only immunomodulator in the analysis, it was assumed to have the same withdrawal rate as topical aminosalicylates. Uncertainty surrounding estimates of withdrawal rates was explored in probabilistic sensitivity analysis.

Calculating probability of remission conditional on non-withdrawal

The results of the network meta-analyses are summarised in Appendix I with remission rates presented as odds ratios and withdrawal rates as hazard ratios. As withdrawal, remission and non-remission are treated as mutually exclusive events, the following approach was used to calculate the probability of remission and non-remission conditional on non-withdrawal from treatment in the cost-effectiveness model:

Probability of withdrawal

BH and HR are the baseline hazard and treatment-specific hazard ratio for withdrawal due to adverse events; let θ_w denote the treatment-specific instantaneous rate of withdrawal on a log scale and P_w the probability of withdrawal (assuming a constant rate) over time period t. Then:

$$\theta_w = ln[BH] + ln[HR]$$

$$P_w = 1 - exp\left[-exp\left(\theta_{w)} * t\right]\right.$$

Probability of remission

BO and OR are the baseline odds of remission and the treatment-specific odds of remission; let θ_r denote the treatment-specific log odds for remission and P_r the probability of remission. Then:

$$\theta_r = ln[BO] + ln[OR]$$

$$P_r = \frac{exp\,[\theta_r]}{1 + exp\,[\theta_r]}$$

Let $P_{r|w^c}$ denote the probability of remission conditional on non-withdrawal. Then:

$$P_{r|w^c} = P_r * [1 - P_w]$$

Let $P_{nr|w^c}$ denote the probability of non-remission conditional on non-withdrawal. Then:

$$P_{nr|w^c} = 1 - (P_w + P_{r|w^c})$$

An alternate approach to estimating the probability of remission conditional on non-withdrawal would have been to fit a conditional logistic regression model in the network meta-analysis using RCTs that reported both outcomes. However, as such studies formed a minority of the available RCTs, it would be unduly wasteful to discard all the other evidence. We recognise that the approach described above biases the remission probabilities downward by a small amount; however, because withdrawal rates are generally low for all treatments, we concluded that the bias that would be introduced to the analysis by treating the probabilities as sequential and conditional would be relatively minor and would be by nature conservative. An additional alternative would have been to treat the probabilities as independent; this would have had the advantage of not biasing the point-estimate for remission downwards; however, it would have been necessary to introduce an artificial constraint to prevent probabilities summing to >1 in probabilistic sampling, which would bias results in a much more unpredictable way.

Table 55 summarises the absolute probabilities of withdrawal and of remission and non-remission conditional on non-withdrawal used in the base case cost-effectiveness analyses.

Table 55: Absolute probabilities of withdrawal due to adverse events and remission and non-remission conditional on non-withdrawal

Treatment	Probability withdrawal	Probability remission	Probability non-remission	Evidence network (remission relative effect)
Extensive disease				
HD oASA	2.1%	48.5%	49.4%	5-8 weeks
HD oASA + tASA	1.3%[a]	68.3%	30.4%	5-8 weeks
LD oASA	3.4%	38.1%	58.5%	5-8 weeks
oCS (pred) ± LD oASA	3.8%[b]	62.8%[c]	33.5%	0-4 weeks
oCS (beclo) + LD oASA	0.4%	69.3%	30.3%	0-4 weeks
oCS (bude) ± LD oASA	3.8%	27.3%	68.9%	5-8 weeks
Proctosigmoiditis and left-sided disease				
tASA	0.7%	80.3%	19.0%	0-4 weeks
LD oASA	3.4%	34.4%	62.2%	5-8 weeks
HD oASA	2.1%	40.7%	57.2%	5-8 weeks
LD oASA + tASA	1.3%	45.3%	53.4%	5-8 weeks
oCS (pred) ± LD oASA	3.8%[b]	55.5%[c,d]	40.7%	5-8 weeks
oCS (beclo) + LD oASA	0.4%	45.9%	53.7%	0-4 weeks
oCS (bude) ± LD oASA	3.8%	29.7%	66.5%	5-8 weeks
tCS (pred) ± LD oASA	3.8%[e]	71.2%	25.0%	0-4 weeks
tCS (bude) ± LD oASA[f]	7.4%	40.1%	52.5%	5-8 weeks
tCS (hydro) ± LD oASA[f]	7.4%[e]	39.1%	53.5%	5-8 weeks

Treatment	Probability withdrawal	Probability remission	Probability non-remission	Evidence network (remission relative effect)
Proctitis				
tASA	0.7%	90.5%	8.8%	0-4 weeks
LD oASA	3.4%	40.0%	56.6%	5-8 weeks
Topical tacrolimus	1.3%[g]	85.8%	12.9%	5-8 weeks
LD oASA + tASA	1.3%	51.2%[h]	47.5%	5-8 weeks
oCS (pred) ± LD oASA	3.8%[b]	55.2%[c,d]	41.0%	0-4 weeks
oCS (beclo) + LD oASA	0.4%	65.8%[h]	33.8%	0-4 weeks
oCS (bude) ± LD oASA	3.8%	34.9%[h]	61.3%	5-8 weeks
tCS (pred) ± LD oASA	3.8%[e]	83.3%[h]	12.9%	0-4 weeks

LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; hydro = hydrocortisone

(a) In the absence of withdrawal data, assumed equivalent to LD oASA + tASA
(b) In the absence of withdrawal data, assumed equivalent to oCS (bude) ± LD oASA
(c) Relative effectiveness derived from earlier time point than specified duration in clinical practice
(d) Relative effectiveness derived from extensive disease
(e) In the absence of withdrawal data, assumed equivalent to tCS (bude) ± LD oASA
(f) Not included in base case analysis; only modelled in sensitivity analysis where duration of treatment is set to maximum duration across RCTs
(g) In the absence of withdrawal data, assumed equivalent to tASA
(h) Relative effectiveness derived from proctosigmoiditis and left-sided disease

L.2.5.13 Health-state utilities

Health-state utility values were sourced from published literature in order to estimate QALYs in the cost-effectiveness model. Utility values reflecting active mild-to-moderate disease, remission and severe relapse were taken from Poole (2010), which mapped disease severity measured in 2 RCTs using the Ulcerative Colitis Disease Activity Index (UCDAI) to the EQ-5D.

In the cost-effectiveness model, a proportion of patients were assumed to withdraw from treatment due to adverse events. A search of the published literature did not identify any utility values that quantified the impact of treatment-specific adverse events on quality of life in ulcerative colitis patients. Instead, an estimate of the disutility associated with the use of systemic corticosteroids across a variety of medical conditions was obtained from Sullivan (2016). According to the Summary Product of Characteristics for oral mesalazine, the most common side effects reported are gastrointestinal, including nausea, diarrhoea and abdominal pain. Therefore, an estimate of the disutility associated with gastrointestinal side effects of treatments for osteoporosis served as a proxy for the disutility associated with withdrawal from oral aminosalicylates (Modi 2017).

Table 56: Health state utility values used in the cost-effectiveness model

Health state	Source	Value
Mild to moderate disease	Poole 2010	0.775
Remission	Poole 2010	0.940
Severe relapse	Poole 2010	0.660
Disutility adverse events on oral ASAs	Modi 2017	-0.040
Disutility adverse events on corticosteroids	Sullivan 2016	-0.047

L.2.5.24 Costs

The model captures 3 main categories of costs:

- Drug costs for induction of remission
- Drug costs for maintenance treatment following remission
- Other healthcare resource use

A description of the assumptions about costs and remission rates associated with rescue therapy are summarised separately below.

Drug costs for induction of remission

Drug costs were obtained from the online version of the British National Formulary (BNF) in November 2017. For mesalazine, multiple oral preparations and multiple topical preparations are available. Estimates of the probability of withdrawal and remission for oral and topical aminosalicylates were modelled at the class level so, to keep the total number of treatment sequences in the model to a reasonable level, a practical decision was made not to define separate sequences for each of the different mesalazine preparations. Instead, the volume of prescriptions across different mesalazine preparations was obtained from NHS Prescription Cost Analysis data (November 2017) and used to estimate a weighted average cost per week. For oral mesalazine, separate weekly weighted average costs were estimated for low-dose and high-dose regimens. For topical mesalazine, weighted average costs in proctosigmoiditis, left-sided and extensive disease excluded suppositories as these preparations are only used in proctitis.

Table 57: Weighted average cost per week for low-dose oral mesalazine

Drug	Dose	Cost per week	Weighting	Weighted cost
Mesalazine Tab E/C 400mg	2.4g	£7.74	3.8%	£0.29
Mesalazine Tab E/C 800mg	2.4g	£9.42	1.7%	£0.16
Asacol MR Tab E/C 400mg	2.4g	£13.73	14.3%	£1.96
Asacol MR Tab E/C 800mg	2.4g	£13.73	10.2%	£1.41
Pentasa SR Tab 500mg	2g	£8.61	17.0%	£1.46
Pentasa Gran Sach 1g M/R	2g	£6.46	2.7%	£0.17
Pentasa Gran Sach 2g M/R	2g	£8.61	3.9%	£0.34
Pentasa Tab 1g M/R	2g	£8.61	7.4%	£0.64
Salofalk Gran Sach G/R 500mg M/R	1.5g	£5.70	0.5%	£0.03
Salofalk Gran Sach G/R 1.5g M/R	1.5g	£5.70	1.2%	£0.07
Salofalk Tab G/R 500mg	1.5g	£6.80	0.6%	£0.04
Mezavant XL Tab G/R 1.2g	2.4g	£10.02	10.1%	£1.01

Drug	Dose	Cost per week	Weighting	Weighted cost
Octasa MR Tab E/C 800mg	2.4g	£9.42	11.2%	£1.05
Octasa MR Tab E/C 400mg	2.4g	£7.74	15.5%	£1.20
Weighted average cost per week				**£9.82**

Table 58: Weighted average cost per week for high-dose oral mesalazine

Drug	Dose	Cost per week	Weighting	Weighted cost
Mesalazine Tab E/C 400mg	4.8g	£15.47	3.9%	£0.60
Mesalazine Tab E/C 800mg	4.8g	£18.84	1.8%	£0.34
Asacol MR Tab E/C 400mg	4.8g	£27.45	14.7%	£4.03
Asacol MR Tab E/C 800mg	4.8g	£27.45	10.5%	£2.89
Pentasa SR Tab 500mg	4g	£17.21	17.5%	£3.01
Pentasa Gran Sach 1g M/R	3g	£12.91	2.8%	£0.36
Pentasa Tab 1g M/R	4g	£17.22	7.6%	£1.31
Pentasa Gran Sach 4g M/R	3g	£17.22	0.3%	£0.05
Salofalk Gran Sach G/R 1g M/R	3g	£12.07	1.1%	£0.14
Salofalk Tab G/R 500mg	3g	£13.60	0.6%	£0.08
Salofalk Gran Sach G/R 3g M/R	3g	£11.40	1.4%	£0.16
Mezavant XL Tab G/R 1.2g	4.8g	£20.04	10.4%	£2.08
Octasa MR Tab E/C 800mg	4.8g	£18.84	11.5%	£2.17
Octasa MR Tab E/C 400mg	4.8g	£15.47	16.0%	£2.47
Weighted average cost per week				**£19.68**

Table 59: Weighted average cost per week for topical mesalazine (proctitis)

Drug	Dose	Cost per week	Weighting	Weighted cost
Mesalazine Suppos 500mg	1g	£6.75	10.8%	£0.73
Mesalazine Suppos 250mg	1g	£6.75	2.4%	£0.16
Mesalazine Foam Aero Enem 1g/D	1g	£15.09	8.1%	£1.22
Mesalazine Enem 2g In 59ml	2g	£29.92	4.1%	£1.23
Asacol Suppos 500mg	1g	£6.75	7.8%	£0.53
Asacol Suppos 250mg	1g	£6.75	1.7%	£0.12
Asacol Foam Aero Enem 1g/D	1g	£15.09	1.4%	£0.20
Pentasa Enem 1g In 100ml	1g	£17.73	5.5%	£0.97
Pentasa Suppos 1g	1g	£10.00	35.6%	£3.57
Salofalk Suppos 500mg	1g	£6.75	1.1%	£0.07
Salofalk Enem (2g/59ml)	2g	£29.92	6.0%	£1.81
Salofalk Foam Aero Enem 1g/D	1g	£15.09	3.9%	£0.58
Salofalk Suppos 1g	1g	£10.00	11.6%	£1.16
Weighted average cost per week				**£12.35**

Table 60: Weighted average cost per week for topical mesalazine (proctosigmoiditis, left-sided and extensive disease)

Drug	Dose	Cost per week	Weighting	Weighted cost
Mesalazine Foam Aero Enem 1g/D	2g	£30.17	27.9%	£8.43

Drug	Dose	Cost per week	Weighting	Weighted cost
Mesalazine Enem 2g In 59ml	2g	£29.92	14.2%	£4.25
Asacol Foam Aero Enem 1g/D	2g	£30.17	4.7%	£1.41
Pentasa Enem 1g In 100ml	1g	£17.73	18.9%	£3.35
Salofalk Enem (2g/59ml)	2g	£29.92	20.9%	£6.26
Salofalk Foam Aero Enem 1g/D	2g	£30.17	13.4%	£4.04
Weighted average cost per week				**£27.73**

The costs of all other drugs for the induction of remission are summarised in Table 61. For topical prednisolone, 3 different preparations were available. The lowest cost formulation (prednisolone liquid enema) was used in the base case but sensitivity analyses were run varying the cost to £77.06 per week to reflect the cost of prednisolone suppositories in proctitis and to £93.50 per week to reflect the cost of prednisolone foam enemas in proctosigmoiditis and left-sided disease.

The cost per week for topical tacrolimus was based on the description of the dose and formulation of the drug administered as an ointment in the trial by Lawrance 2017. The committee commented that this does not reflect current practice in the UK and that topical tacrolimus is more likely to be prepared in suppository form as a special on a case by case basis. The cost of compounding this formulation was considered in a sensitivity anlaysis.

Table 61: Cost per week for other drugs for the induction of remission

Drug	Dose	Cost per week
Oral aminosalicylates		
Balsalazide 750mg	6.75g	£14.74
Olsalazine 250mg	2g	£75.13
Oral corticosteroids		
Prednisolone 5 mg	40mg tapering over 8 weeks	£0.88
Beclometasone 5mg M/R	5mg	£13.20
Budesonide 9mg M/R	9mg	£17.50
Topical corticosteroids		
Prednisolone liquid enema 20mg/100ml	20mg	£7.50
Prednisolone suppository 5mg	10mg	£77.06
Prednisolone foam enema 20mg	20mg	£93.50
Budesonide foam enema 2mg	2mg	£28.56
Hydrocortisone foam enema 10%	100mg	£4.67
Immunomodulators		
Tacrolimus ointment 0.1%[a]	3mg	£16.55
Tacrolimus suppository 2mg[b]	2mg	£47.56

(a) As described in the trial by Lawrance 2017

(b) Formulated on a case by case basis assuming 2mg suppository made from 2x1mg capsules requiring 20 minutes of Band 6 pharmacist time per 4-week supply (PSSRU 2017)

Drugs costs for maintenance treatment following remission

In the cost-effectiveness model, once remission is achieved, an assumption was made that, in order to maintain remission for the duration of the analysis, a proportion of people would

receive maintenance treatment. An assumption about the proportion of people receiving either low-dose oral aminosalicylates or azathioprine as maintenance treatment was based on the findings of a small audit of 4 practices in South West London (Alexakis 2016) and validated with the committee. It was assumed that maintenance treatment contributed to the costs in people whose disease had entered remission but did not have any additional effect on health outcomes. Disease relapse was not modelled due to the short time horizon for the analysis.

Table 62: Assumptions about the proportion of people receiving maintenance treatment and the weekly cost

Assumption	%	Dose	Cost per week
% of patients low-dose mesalazine	41%	2.4g	£9.82
% of patients low-dose on azathioprine	20%	2mg/kg[a]	£0.84

(a) Average body weight 77kg

Healthcare resource use

Estimates of ulcerative colitis-related healthcare resource use for people with active disease and disease in remission were obtained from a published retrospective chart review that recruited patients from 33 general practitioner and 34 gastroenterologist sites in the UK (Bodger 2014). The study included patients who had been diagnosed with mild-to-moderate ulcerative colitis at least 1 year prior to the inception date. Resource use estimates were combined with relevant unit costs sourced from the PSSRU and NHS Reference Costs.

Table 63: Other healthcare resource use assumptions

Resource type	Active disease	Remission	Unit cost	Source
GP appointments (9.22 minutes each) per year- mean (SD)	2.00 (2.10)	0.80 (1.00)	£38.00	PSSRU 2017
Outpatient appointments per year – mean (SD)	3.20 (1.40)	1.00 (1.00)	£137.37	NHS Ref Costs 2016/2017 [301]
Specialist nurse appointments per year – mean (SD)	1.00 (1.60)	0.20 (0.60)	£68.00	NHS Ref Costs 2016/2017 [N29AF]
A&E attendance (%)	15%	0%	£148.36	NHS Ref Costs 2016/2017 [180]
Outpatient procedure (%)	26%	7%	£210.63	NHS Ref Costs 2016/2017 [FE35Z, FE32Z]

L.2.3.5 Rescue therapy

In the cost-effectiveness model, if remission had not been induced after 3 lines of treatment (up to 4 lines in proctitis), it was assumed the person would require hospitalisation and receive rescue therapy to treat severe ulcerative colitis. The scope of this review question and cost-effectiveness analysis is restricted to the induction of remission for mild-to-moderate ulcerative colitis; therefore, no systematic reviews of the literature were undertaken to evaluate the comparative effectiveness of individual treatments that were included as part of rescue therapy. Instead, assumptions about response to rescue therapy are based on the

2014 IBD national clinical audit of inpatient care and the 2016 IBD national clinical audit of biological therapies. The assumptions about rescue therapy were the same across all arms in the cost-effectiveness model.

Figure 37: Structure of rescue therapy assumptions in the cost-effectiveness model

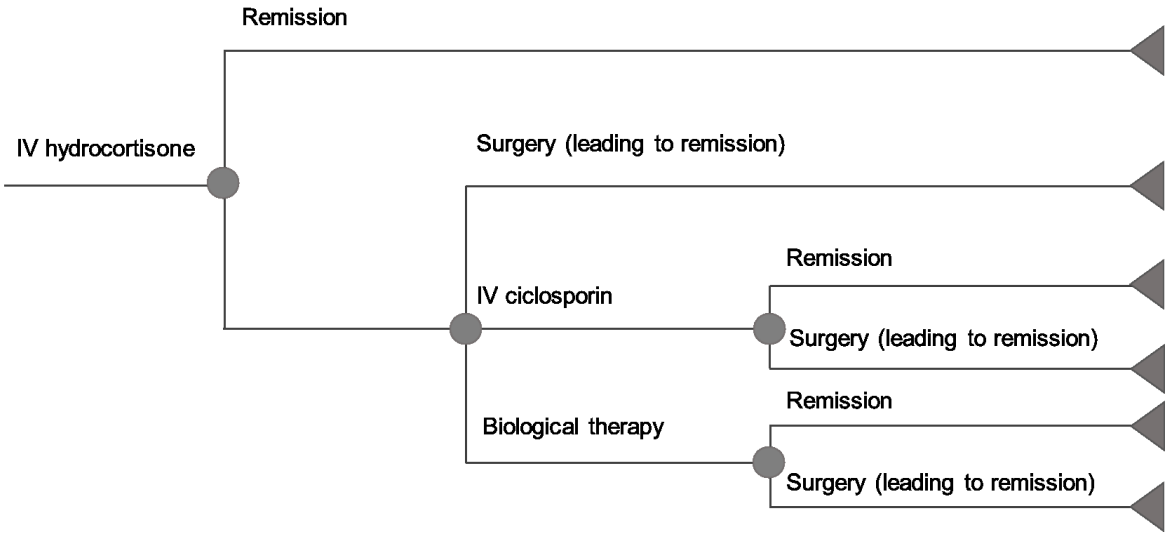


Table 64: Assumptions for response to rescue therapy

Treatment	Response	Source
IV hydrocortisone	65%	IBD national clinical audit of inpatient care 2014
IV ciclosporin	27%	IBD national clinical audit of inpatient care 2014
Biological therapy	85%	IBD national clinical audit of inpatient care 2014
Surgery	100%	Assumption

Table 65: Dose and cost of biological therapies

Drug	Cost induction (6 weeks)[a]	Maintenance dose	Cost per week maintenance (8 weeks)	Proportion on each drug[b]
Adalimumab 40mg/0.4mL	£4930	40mg every 2 weeks	£352	20%
Golimumab 50mg/0.5mL	£3052[c]	50mg every 4 weeks	£191	8%
Infliximab 100mg (originator)	£5035	5mg/kg every 8 weeks	£227	36%
Infliximab 100mg (biosimilar)	£4524	5mg/kg every 8 weeks	£206	28%
Vedolizumab 300mg	£6150[d]	300mg every 8 weeks	£256	9%
Weighted average cost across all biological agents	**£5084**		**£246**	

Drug	Cost induction (6 weeks)[a]	Maintenance dose	Cost per week maintenance (8 weeks)	Proportion on each drug[b]

(a) As per BNF, assuming average body weight 77kg
(b) IBD national clinical audit 2016
(c) As per NICE TA329, assumes 100 mg dose of golimumab provided at the same cost as the 50 mg dose under a patient acces scheme
(d) Patient access scheme discount not applied (commercial in confidence)

Table 66: Combined cost and durations for each branch of rescue therapy

Treatment sequence	Time to remission (weeks)	Cost	Source
IV hydrocortisone	0.43	£1957	NHS Ref Costs 2016/2017 [FD02E-H]
IV hydrocortisone followed by surgery	1	£3456	NHS Ref Costs 2016/2017 [FD02C-D]
IV hydrocortisone followed by IV ciclosporin	1	£3456	NHS Ref Costs 2016/2017 [FD02C-D]
IV hydrocortisone followed by IV ciclosporin and surgery	2	£7242	NHS Ref Costs 2016/2017 [FD02A-B]
IV hydrocortisone followed by biological therapy (induction phase)	6.5	£7042	NHS Ref Costs 2016/2017 [FD02E-H]; weighted average cost of biological therapies (Table 16)
IV hydrocortisone followed by biological therapy (induction phase) and surgery	7.5	£10,497	NHS Ref Costs 2016/2017 [FD02C-H]; weighted average cost of biological therapies (Table 16)

In the base case, it was assumed that response to treatment for people receiving biological therapies is assessed at 6 weeks. In people whose disease is responding, maintenance treatment would continue for an additional 8 weeks. However, the committee indicated that in clinical practice, treatment would likely continue beyond 14 weeks and therefore a sensitivity analysis was run in which people whose disease had entered remission continued to receive biological therapy for the remaining time horizon of the model.

L.2.596 Sensitivity analysis

Probabilistic sensitivity analyses

To take parameter uncertainty into account, probability distributions were estimated for all input variables with the exception of:

- Duration of treatment for induction of remission – these were assumed to be fixed in the model but different assumptions are explored in structural sensitivity analyses described below
- Duration of treatment for rescue therapies
- Cost of biological therapies

Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated based on the properties of the specific type of data. Beta distributions are used for variables denoting a probability, as bounded between 0 and 1 where data are reported to estimate the standard error, otherwise a triangular distribution is estimated. A beta distribution is also estimated for utility values, which are also traditionally confined to values between 0 and 1. Gamma distributions are used to represent uncertainty in cost parameters, which are non-negative and often highly skewed. A summary of all parameters and the distributions assumed in probabilistic analysis is provided in Table 67.

Drug costs for the induction of remission were entered in the model as weekly costs. A decision was made to introduce uncertainty into the estimates of weekly drug costs by estimating standard errors equal to 0.20 of the mean and fitting gamma distributions. This was done for two reasons:

- For several drugs, a number of different preparations are available and the prescription volumes used to estimate weighted average costs are subject to uncertainty. Allowing for uncertainty in weekly drug costs can serve as a simple proxy for variation in prescribing patterns and adherence.
- Durations of treatment in the model are assumed to be fixed and class-level effects were assumed for aminosalicylates. If costs were not subject to uncertainty, within-class ranking of treatments would be preserved 100% of the time, leading to an artificially high level of certainty in results.

Monte Carlo simulation was used to randomly sample 1,000 times from all available distributions. Results are presented using cost-effectiveness acceptability curves (CEACs), which show the probability that a given sequence is more cost effective than the alternative sequences over a range of threshold values.

Table 67: Summary of assumptions for parameter uncertainty used in probabilistic sensitivity analyses

Parameter	Point estimate	Distribution	Parameters	Source
Withdrawal all extents of disease				
Baseline ln(rate)				
LD oASA	-0.806	Normal	μ = -0.806 σ = 0.104	Baseline synthesis[(a)]
ln(HR) vs. LD oASA				
HD oASA	-0.481	Multivariate normal		NMA
tASA	-0.940	Multivariate normal		NMA
HD oASA + tASA	-0.966	Multivariate normal		NMA
oCS (beclo) + LD oASA	-1.469	Multivariate normal		NMA
oCS (bude)	0.116	Multivariate normal		NMA
tCS (bude)	0.805	Multivariate normal		NMA
Remission proctitis 0-4 weeks				
Baseline probability				
LD oASA	0.414	Beta	α = 12 β = 17	Gionchetti 1998
ln(OR) vs LD oASA				
tASA vs. LD oASA	2.681	Multivariate normal		NMA
Placebo vs. LD oASA	0.686	Multivariate normal		NMA
Remission proctitis 5-8 weeks				

Parameter	Point estimate	Distribution	Parameters	Source
Baseline ln(odds)				
LD oASA	-0.635	Normal	μ = -0.635 σ = 0.151	Ito 2010
ln(OR) vs. LD oASA				
tASA	-1.179	Multivariate normal		NMA
Topical tacrolimus	2.246	Multivariate normal		NMA
Placebo	-1.782	Multivariate normal		NMA
Remission: proctosigmoiditis and left-sided disease 0-4 weeks				
Baseline ln(odds)				
LD oASA	-1.169	Normal	μ = -1.169 σ = 0.100	Baseline synthesis[(b)]
ln(OR) vs. LD oASA				
oCS (beclo)	-0.379	Multivariate normal		NMA
HD oASA	0.409	Multivariate normal		NMA
tASA	2.610	Multivariate normal		NMA
oCS (beclo) + LD oASA	1.012	Multivariate normal		NMA
Placebo	-0.280	Multivariate normal		NMA
tCS (pred)	2.211	Multivariate normal		NMA
Remission: proctosigmoiditis and left-sided disease 5-8 weeks				
Baseline ln(odds)				
LD oASA	-0.592	Normal	μ = -0.592 σ = 0.057	Baseline synthesis[(c)]
ln(OR) vs. LD oASA				
oCS (bude)	-0.216	Multivariate normal		NMA
tCS (bude)	0.324	Multivariate normal		NMA
HD oASA	0.254	Multivariate normal		NMA
tCS (hydro)	0.280	Multivariate normal		NMA
LD oASA + tASA	0.427	Multivariate normal		NMA
tASA	0.740	Multivariate normal		NMA
Placebo	-0.638	Multivariate normal		NMA
Remission: extensive disease 0-4 weeks				
Baseline ln(odds)				
LD oASA	-0.220	Normal	μ = -0.220 σ = 0.325	Baseline synthesis[(d)]
ln(OR) vs. LD oASA				
oCS (beclo)	1.047	Multivariate normal		NMA
HD oASA	0.410	Multivariate normal		NMA
HD oASA + tASA	0.838	Multivariate normal		NMA
oCS (pred)	0.648	Multivariate normal		NMA
Remission: extensive disease 5-8 weeks				
Baseline ln(odds)				
HD oASA	-0.019	Normal	μ = -0.019 σ = 0.208	Baseline synthesis[(e)]

Parameter	Point estimate	Distribution	Parameters	Source
ln(OR) vs. HD oASA				
oCS (bude)	-0.907	Multivariate normal		NMA
HD oASA + tASA	0.830	Multivariate normal		NMA
Health state utilities				
Remission	0.940	Beta	α = 22627.813 β = 1444.329	Poole 2010
Active disease	0.775	Beta	α = 864.093 β = 250.866	Poole 2010
Severe relapse	0.660	Beta	α = 133.999 β = 69.030	Poole 2010
Treatment-related adverse event disutilities				
Aminosalicylates	-0.040	Triangular	Min = -0.08 Mode = -0.04 Max = 0	Modi 2017
Corticosteroids	-0.047	Triangular	Min = -0.094 Mode = -0.047 Max = 0	Sullivan 2016
Surgery	-0.100	Triangular	Min = -0.2 Mode = -0.1 Max = 0	Argueda 2004
Drug costs				
Proctitis				
LD oASA	£9.82	Gamma	α = 25.00 β = 0.393	BNF, NHS PCA data (Nov 2017)
tASA	£12.35	Gamma	α = 25.000 β = 0.494	BNF, NHS PCA data (Nov 2017)
oCS (pred)	£0.88	Gamma	α = 25.000 β = 0.035	BNF (Nov 2017)
oCS (bude)	£15.92	Gamma	α = 25.000 β = 1.142	BNF (Nov 2017)
tCS (pred liquid enema)	£7.50	Gamma	α = 25.000 β = 0.300	BNF (Nov 2017)
tCS (pred suppository)	£64.85	Gamma	α = 25.000 β = 2.594	BNF (Nov 2017)
Topical tacrolimus (ointment)	£16.55	Gamma	α = 25.000 β = 0.662	BNF (Nov 2017)
Topical tacrolimus (suppository)	£47.56	Gamma	α = 25.000 β = 1.902	BNF (Nov 2017), PSSRU 2017 (pharmacist cost)
LD oASA + tASA	£22.17	Gamma	α = 25.000 β = 0.887	BNF, NHS PCA data (Nov 2017)
LD oASA + oCS (pred)	£10.70	Gamma	α = 25.000 β = 0.428	BNF, NHS PCA data (Nov 2017)
LD oASA + oCS (beclo)	£23.02	Gamma	α = 25.000 β = 0.921	BNF, NHS PCA data (Nov 2017)

Parameter	Point estimate	Distribution	Parameters	Source
LD oASA + oCS (bude)	£25.74	Gamma	α = 25.000 β = 1.030	BNF, NHS PCA data (Nov 2017)
LD oASA + tCS (pred liquid enema)	£17.32	Gamma	α = 25.000 β = 0.693	BNF, NHS PCA data (Nov 2017)
Proctosigmoiditis and left-sided / extensive disease				
LD oASA	£9.82	Gamma	α = 25.00 β = 0.393	BNF, NHS PCA data (Nov 2017)
HD oASA	£19.68	Gamma	α = 25.00 β = 0.787	BNF, NHS PCA data (Nov 2017)
HD oASA (balsalazide)	£14.74	Gamma	α = 25.00 β = 0.590	BNF (Nov 2017)
HD oASA (olsalazine)	£75.13	Gamma	α = 25.00 β = 3.005	BNF (Nov 2017)
tASA	£27.73	Gamma	α = 25.00 β = 1.109	BNF, NHS PCA data (Nov 2017)
oCS (pred)	£0.88	Gamma	α = 25.00 β = 0.035	BNF (Nov 2017)
oCS (bude)	£15.92	Gamma	α = 25.00 β = 0.637	BNF (Nov 2017)
tCS (pred liquid enema)	£7.50	Gamma	α = 25.000 β = 0.300	BNF (Nov 2017)
tCS (pred foam enema)	£93.50	Gamma	α = 25.000 β = 3.740	BNF (Nov 2017)
tCS (hydro)	£4.67	Gamma	α = 25.000 β = 0.187	BNF (Nov 2017)
tCS (bude)	£28.56	Gamma	α = 25.000 β = 1.142	BNF (Nov 2017)
LD oASA + tASA	£37.55	Gamma	α = 25.000 β = 1.502	BNF, NHS PCA data (Nov 2017)
HD oASA + tASA	£47.41	Gamma	α = 25.000 β = 1.896	BNF, NHS PCA data (Nov 2017)
LD oASA + oCS (pred)	£10.70	Gamma	α = 25.000 β = 0.428	BNF, NHS PCA data (Nov 2017)
LD oASA + oCS (beclo)	£23.02	Gamma	α = 25.000 β = 0.921	BNF, NHS PCA data (Nov 2017)
LD oASA + oCS (bude)	£25.74	Gamma	α = 25.000 β = 1.030	BNF, NHS PCA data (Nov 2017)
LD oASA + tCS (pred liquid enema)	£17.32	Gamma	α = 25.000 β = 0.693	BNF, NHS PCA data (Nov 2017)
LD oASA + tCS (pred foam enema)	£103.32	Gamma	α = 25.000 β = 4.133	BNF, NHS PCA data (Nov 2017)
LD oASA + tCS (hydro)	£14.49	Gamma	α = 25.000 β = 0.580	BNF, NHS PCA data (Nov 2017)
LD oASA + tCS (bude)	£38.71	Gamma	α = 25.000	BNF, NHS PCA data (Nov 2017)

Parameter	Point estimate	Distribution	Parameters	Source
			β = 1.548	
Maintenance treatment				
Proportion of people taking				
ASA	0.414	Dirichlet	SE = 0.059	Alexakis 2016
Azathiorprine	0.200		SE = 0.048	
None	0.386		SE = 0.058	
Background healthcare resource use				
Remission (per year)				
GP appointment	0.80	Lognormal	μ = -0.246 σ = 0.212	Bodger 2014
Outpatient appointments	1.00	Lognormal	μ = -0.014 σ = 0.170	Bodger 2014
Nursing face-to-face	0.20	Lognormal	μ = -1.727 σ = 0.485	Bodger 2014
A&E attendance (%)	0.00	-	-	Bodger 2014
Outpatient procedures (%)	0.07	Beta	α = 2 β = 32	Bodger 2014
Active disease				
GP appointment	2.00	Lognormal	μ = 0.685 σ = 0.125	Bodger 2014
Outpatient appointments	3.20	Lognormal	μ = 1.162 σ = 0.052	Bodger 2014
Nursing face-to-face	1.00	Lognormal	μ = -0.018 σ = 0.190	Bodger 2014
A&E attendance (%)	0.15	Beta	α = 11 β = 59	Bodger 2014
Outpatient procedures (%)	0.26	Beta	α = 18 β = 52	Bodger 2014
Unit costs				
Outpatient appointments				
Consultant-led gastroenterology outpatient appt [301]	£141	Gamma	α = 1746.500 β = 0.081	NHS Ref Costs 2016/2017
Non-consultant-led gastroenterology outpatient appt [301]	£107	Gamma	α = 585.645 β = 0.182	NHS Ref Costs 2016/2017
Outpatient procedures				
Diagnostic Flexible Sigmoidoscopy, 19 years and over [FE35Z]	£175	Gamma	α = 70.795 β = 2.475	NHS Ref Costs 2016/2017
Diagnostic Colonoscopy, 19 years and over [FE32Z]	£277	Gamma	α = 37.980 β = 7.301	NHS Ref Costs 2016/2017
Nursing face-to-face [N29AF]	£68	Gamma	α = 282.247 β = 0.241	NHS Ref Costs 2016/2017

Parameter	Point estimate	Distribution	Parameters	Source
A&E attendance [180]	£148	-	-	NHS Ref Costs 2016/2017
Blood test [DAPS03]		Gamma	α = 143.315 β = 0.012	NHS Ref Costs 2016/2017
GP appointment	£38	-	-	PSSRU 2017
Rescue therapy				
Proportion of people responding to IV hydrocortisone	0.652	Beta	α = 2293 β = 1226	UK IBD national clinical audit of inpatient care 2014
Of people not responding to IV hydrocortisone:				
Proportion receiving surgery	0.193	Beta	α = 237 β = 989	UK IBD national clinical audit of inpatient care 2014
Of people not receiving surgery:				
Proportion receiving ciclosporin	0.338	Beta	α = 261 β = 512	UK IBD national clinical audit of inpatient care 2014
Proportion receiving aTNFs	0.662	Beta	α = 512 β = 261	UK IBD national clinical audit of inpatient care 2014
Of people receiving ciclosporin:				
Proportion achieving remission	0.736	Beta	α = 184 β = 66	UK IBD national clinical audit of inpatient care 2014
Proportion requiring surgery	0.264	-	-	Calculated
Of people receiving biological therapy				
Proportion achieving remission	0.848	Beta	α = 425 β = 76	UK IBD national clinical audit of inpatient care 2014
Proportion requiring surgery	0.152	-	-	Calculated
Proportion of people taking each biological therapy				
Adalimumab	0.199	Dirichlet	SE = 0.014	UK IBD national clinical audit of biological therapies 2016
Golimumab	0.076		SE = 0.009	
Infliximab biosimilar	0.278		SE = 0.016	
Infliximab originator	0.357		SE = 0.017	
Vedolizumab	0.090		SE = 0.010	
Cost inpatient admissions (elective)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£9,009	Gamma	α = 72.160 β = 124.849	NHS Ref Costs 2016/2017

Parameter	Point estimate	Distribution	Parameters	Source
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£4,848	Gamma	α = 152.626 β = 31.761	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£4,529	Gamma	α = 94.620 β = 47.861	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£3,393	Gamma	α = 1672.459 β = 2.029	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£2,960	Gamma	α = 266.054 β = 11.125	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£1,700	Gamma	α = 300.944 β = 5.650	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£1,290	Gamma	α = 743.071 β = 1.736	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£828	Gamma	α = 508.533 β = 1.627	NHS Ref Costs 2016/2017
Cost inpatient admissions (elective excess bed-days)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£435	Gamma	α = 4.896 β = 88.793	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£409	-	-	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£269	-	-	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£434	Gamma	α = 34.576 β = 12.552	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£379	Gamma	α = 63.315 β = 5.983	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£371	Gamma	α = 1099.660 β = 0.337	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£309	Gamma	α = 483.196 β = 0.640	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£384	Gamma	α = 260.178 β = 1.476	NHS Ref Costs 2016/2017
Cost inpatient admissions (non-elective)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£8,300	Gamma	α = 1252.396 β = 6.627	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£5,000	Gamma	α = 774.982 β = 6.452	NHS Ref Costs 2016/2017

Parameter	Point estimate	Distribution	Parameters	Source
IBD Single Intervention, CC Score 4+ [FD02C]	£5,050	Gamma	α = 5151.508 β = 0.980	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£2,820	Gamma	α = 12501.295 β = 0.226	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£2,641	Gamma	α = 15831.327 β = 0.167	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£2,134	Gamma	α = 15224.861 β = 0.140	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£1,806	Gamma	α = 31459.911 β = 0.057	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£1,648	Gamma	α = 28362.720 β = 0.058	NHS Ref Costs 2016/2017
Cost inpatient admissions (non-elective excess bed-days)				
IBD Multiple Interventions, CC Score 3+ [FD02A]	£353	Gamma	α = 261.341 β = 1.352	NHS Ref Costs 2016/2017
IBD Multiple Interventions, CC Score 0-2 [FD02B]	£396	Gamma	α = 196.123 β = 2.022	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 4+ [FD02C]	£321	Gamma	α = 190.149 β = 1.689	NHS Ref Costs 2016/2017
IBD Single Intervention, CC Score 0-3 [FD02D]	£329	Gamma	α = 1033.307 β = 0.318	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 5+ [FD02E]	£304	Gamma	α = 1545.016 β = 0.197	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 3-4 [FD02F]	£294	Gamma	α = 2571.506 β = 0.114	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 1-2 [FD02G]	£294	Gamma	α = 3172.810 β = 0.093	NHS Ref Costs 2016/2017
IBD without Interventions, CC Score 0 [FD02H]	£299	Gamma	α = 2813.486 β = 0.106	NHS Ref Costs 2016/2017

LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; hydro = hydrocortisone

(a) See Appendix I, Table 46 for list of studies that informed baseline synthesis
(b) See Appendix I, Table 30 for list of studies that informed baseline synthesis
(c) See Appendix I, Table 34 for list of studies that informed baseline synthesis
(d) See Appendix I, Table 38 for list of studies that informed baseline synthesis
(e) See Appendix I, Table 42 for list of studies that informed baseline synthesis

Scenario analyses

A number of scenario analyses were conducted in order to explore the impact of several assumptions on model results:

- **SA1: Duration of treatment set to maximum of all RCTs for each drug**

  For certain drugs, the committee specified that the duration of treatment in clinical practice would be shorter than the most frequently reported duration of follow-up in RCTs. This meant that, in the base case, sequences containing topical hydrocortisone or topical budesonide could not be modelled in proctosigmoiditis and left-sided disease. In this sensitivity analysis, the duration for each treatment is set to the maximum duration of follow-up reported in RCTs for each drug and allows all 75 sequences listed in Table 51

- **SA2: No early switching of treatments in the event of non-remission**

  This scenario analysis (which reverts the analysis to the approach used the 2013 guideline model) was run for each extent of disease and assumed there is no early assessment of response to treatment. All people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome is remission or non-remission.

- **SA3: Duration of maintenance on biological therapies**

  In this scenario analysis, people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model. This scenario anlaysis was run for all extents of disease.

- **SA4: Vary drug prices for topical prednisolone and topical tacrolimus**

  This scenario analysis was run in proctitis varying the price of topical prednisolone from £7.50 (liquid enema) to £77.06 (suppository) and the price of topical tacrolimus from £16.55 (ointment) to £47.56 (suppository). A scenario analysis was also run in proctosigmoiditis and left-sided disease varying the price of topical prednisolone from £7.50 (liquid enema) to £93.50 (foam enema).

L.3 Results

Results for proctosigmoiditis and left-sided disease are presented first because this is the extent of disease with the largest number of treatment sequences and the most RCT evidence available to estimate relative treatment effects. This is followed by results in proctitis; due to the limited number of RCTs that were conducted specifically in people with proctitis, it was necessary to borrow information on the relative effectiveness of a number of treatments from other extents of disease. Results in extensive disease are presented last.

L.3.1 Proctosigmoiditis and left-sided disease

L.3.1.1 Remission by line of treatment

Table 68 shows the proportion of people whose disease is predicted to enter clinical remission in each line of treatment for each sequence in the base-case analysis for proctosigmoiditis and left-sided disease. Sequences containing topical hydrocortisone or topical budesonide were omitted from the base-case analysis (see L.2.4). Sequences that begin with topical aminosalicylate (PLS31–PLS34) have the highest proportion of people entering remission in first line (80.3%) and the lowest proportion of people requiring rescue therapy (3.1–7.6%) with on average 3.0–3.3 weeks out of a total time horizon of 30 weeks spent in an active disease state.

Table 68 also shows the costs of each treatment sequence broken down into the following categories: cost of drugs for induction of remission, cost of rescue therapy, cost of other healthcare resource use (consultant, nurse, GP, outpatient appointments, A&E attendances and blood tests) and cost of maintenance treatment. The widest variation in absolute costs is seen with rescue therapy (range £99 – £1,204). In other words, the proportion of patients requiring rescue therapy accounts for the biggest differences in costs when comparing treatment sequences.

Table 68: Proportion of people whose disease enters remission by line of treatment, average time spent in active disease vs. remission and breakdown of costs for each treatment sequence in the base-case analysis for proctosigmoiditis and left-sided disease (excludes sequences with topical budesonide and topical hydrocortisone)

Treatment sequence		Proportion entering remission				Weeks active	Weeks remission	Costs				
		1st line	2nd line	3rd line	Rescue			Drug	Rescue	Other healthcare	Maintenance	Total
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	34.4%	26.5%	21.7%	17.4%	8.4	21.6	£158	£549	£112	£364	£1,183
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	34.4%	26.5%	18.2%	20.9%	7.7	22.3	£159	£660	£119	£367	£1,305
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	34.4%	26.5%	11.6%	27.5%	8.5	21.5	£184	£867	£113	£378	£1,543
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	34.4%	26.7%	21.6%	17.3%	8.3	21.7	£148	£546	£112	£364	£1,169
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	34.4%	26.7%	18.0%	20.8%	7.7	22.3	£148	£657	£119	£366	£1,291
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	34.4%	26.7%	11.5%	27.3%	8.5	21.5	£173	£863	£113	£378	£1,527
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	34.4%	26.5%	27.8%	11.3%	7.5	22.5	£156	£356	£119	£354	£984
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	34.4%	26.7%	27.7%	11.2%	7.5	22.5	£145	£354	£119	£353	£971
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	34.4%	29.3%	20.1%	16.1%	8.2	21.8	£223	£509	£112	£359	£1,203
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	34.4%	29.3%	16.9%	19.4%	7.6	22.4	£224	£612	£119	£361	£1,315
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	34.4%	29.3%	10.8%	25.5%	8.4	21.6	£247	£805	£114	£371	£1,537
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	34.4%	29.5%	20.0%	16.0%	8.2	21.8	£212	£506	£112	£358	£1,189

Treatment sequence		Proportion entering remission				Weeks active	Weeks remission	Costs				
		1st line	2nd line	3rd line	Rescue			Drug	Rescue	Other healthcare	Maintenance	Total
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	34.4%	29.5%	16.7%	19.3%	7.6	22.4	£213	£609	£119	£360	£1,301
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	34.4%	29.5%	10.7%	25.4%	8.4	21.6	£237	£800	£114	£371	£1,521
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	34.4%	29.3%	25.8%	10.5%	7.4	22.6	£221	£330	£119	£348	£1,019
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	34.4%	29.5%	25.6%	10.4%	7.4	22.6	£211	£328	£119	£348	£1,006
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	40.7%	26.6%	22.9%	9.8%	7.2	22.8	£254	£308	£120	£333	£1,015
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	40.7%	26.6%	15.0%	17.7%	7.3	22.7	£257	£557	£120	£344	£1,278
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	40.7%	26.6%	9.7%	23.0%	8.0	22.0	£278	£725	£115	£353	£1,471
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	40.7%	26.6%	23.2%	9.4%	7.1	22.9	£254	£297	£120	£332	£1,004
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	80.3%	8.8%	6.0%	4.8%	3.3	26.7	£148	£152	£149	£229	£679
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	80.3%	8.8%	5.0%	5.8%	3.1	26.9	£149	£184	£151	£230	£714
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	80.3%	8.8%	3.2%	7.6%	3.3	26.7	£156	£241	£150	£233	£779
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	80.3%	8.8%	7.7%	3.1%	3.0	27.0	£148	£99	£151	£226	£624
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	45.3%	30.7%	0.1%	23.9%	6.5	23.5	£253	£754	£125	£298	£1,430

Treatment sequence		Proportion entering remission				Weeks active	Weeks remission	Costs				
		1st line	2nd line	3rd line	Rescue			Drug	Rescue	Other healthcare	Maintenance	Total
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	45.3%	25.6%	0.1%	29.0%	5.6	24.4	£254	£915	£135	£302	£1,606
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	45.3%	16.9%	0.1%	37.8%	6.8	23.2	£289	£1,191	£127	£317	£1,924
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	45.3%	39.1%	0.2%	15.5%	5.3	24.7	£250	£489	£135	£284	£1,157
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	45.3%	30.1%	0.5%	24.2%	6.6	23.4	£253	£762	£124	£300	£1,439
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	45.3%	25.0%	0.4%	29.4%	5.6	24.4	£254	£926	£135	£303	£1,618
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	45.3%	16.3%	0.3%	38.2%	6.8	23.2	£289	£1,204	£126	£319	£1,939
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	45.3%	38.5%	0.6%	15.7%	5.4	24.6	£250	£494	£134	£285	£1,163
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	71.2%	9.9%	10.5%	8.4%	4.0	26.0	£52	£266	£145	£260	£723
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (beclo)	71.2%	9.9%	8.8%	10.1%	3.7	26.3	£53	£320	£148	£261	£782
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	71.2%	9.9%	5.6%	13.3%	4.1	25.9	£65	£420	£146	£267	£897
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	71.2%	11.8%	9.5%	7.6%	3.9	26.1	£68	£240	£145	£256	£709
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (beclo)	71.2%	11.8%	7.9%	9.2%	3.6	26.4	£68	£290	£148	£257	£764
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	71.2%	11.8%	5.1%	12.0%	4.0	26.0	£79	£379	£146	£262	£867
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	71.2%	13.1%	8.8%	7.0%	3.8	26.2	£98	£222	£145	£253	£719

Treatment sequence		Proportion entering remission				Weeks active	Weeks remission	Costs				
		1st line	2nd line	3rd line	Rescue			Drug	Rescue	Other healthcare	Maintenance	Total
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (beclo)	71.2%	13.1%	7.3%	8.5%	3.6	26.4	£98	£268	£148	£254	£769
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	71.2%	13.1%	4.7%	11.1%	3.9	26.1	£109	£350	£146	£259	£864
Minimum		34.4%	8.8%	0.1%	3.1%	3.0	21.5	£52	£99	£112	£226	£624
Maximum		80.3%	39.1%	27.8%	38.2%	8.5	27.0	£289	£1,204	£151	£378	£1,939

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide

L.3.1.12 Cost-effectiveness results

Table 69 summarises the base-case cost-effectiveness results in proctosigmoiditis and left-sided disease with sequences ordered from least costly to most costly. Treatment sequence PLS31, which begins with a topical aminosalicylate, followed by the addition of an oral aminosalicylate and then oral prednisolone in combination with an oral aminoalicylate is expected to generate more QALYs and incur lower costs than all other treatment sequences except PLS34. However, the difference in QALYs between strategies is very small.

Table 69 also presents the probability that each strategy is cost effective and expected net monetary benefit at a threshold value of £20,000/QALY. Note that at this threshold value, the strategy with the highest probability of being cost effective (PLS34) is not the the strategy with the highest expected net benefit (PLS31). This finding is further illustrated in Figure 38 and Figure 39. Figure 38 presents the cost-effectiveness acceptability curve (CEAC), which shows all treatment strategies with a >3% probability of being cost effective. Figure 39 presents the cost-effectiveness acceptability frontier (CEAF), which plots the probability that the optimal option (as defined by expected net benefit) is cost effective. The switch point in the CEAF where the optimal strategy changes from PLS31 to PLS34 occurs at the ICER between the two options (approximately £37,000/QALY). The results seen here arise from asymmetry in the distributions of expected value (Fenwick 2001). Although there were more model iterations in which PLS34 generated a higher net benefit, in the iterations where PLS31 was superior, it was superior by a greater degree. The only difference between the sequences PLS31 and PLS34 is the mode of administration of the corticosteroid in the third line (oral prednisolone and topical prednisolone respectively). The results of the network meta-analysis showed there was considerable uncertainty in the estimate of the relative effectiveness of topical prednisolone as there was only one small study directly comparing this option to topical aminosaliycylates.

Table 69: Base-case mean probabilistic cost-effectiveness results for proctosigmoiditis and left-sided disease

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£760	0.5283				14.5%	£9,806
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	£785	0.5263	£25	-0.0020	dominated	9.6%	£9,740
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£791	0.5291	£31	0.0008	£37,349	54.1%	£9,792
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	£794	0.5265	£3	-0.0026	dominated	5.4%	£9,737
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	£801	0.5259	£10	-0.0032	dominated	1.1%	£9,718
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£809	0.5291	£18	-0.0001	dominated	5.5%	£9,772

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (beclo)	£853	0.5273	£62	-0.0018	dominated	3.2%	£9,694
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (beclo)	£858	0.5275	£67	-0.0016	dominated	1.9%	£9,693
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (beclo)	£875	0.5271	£84	-0.0021	dominated	0.1%	£9,667
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£894	0.5280	£103	-0.0012	dominated	0.0%	£9,665
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	£969	0.5261	£178	-0.0030	dominated	0.0%	£9,553
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	£975	0.5258	£185	-0.0033	dominated	0.0%	£9,540
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	£1,011	0.5254	£220	-0.0037	dominated	0.0%	£9,497
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,050	0.5159	£259	-0.0132	dominated	0.0%	£9,268
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,064	0.5159	£273	-0.0132	dominated	0.0%	£9,254
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	£1,071	0.5172	£280	-0.0119	dominated	0.0%	£9,274
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,077	0.5162	£286	-0.0130	dominated	0.0%	£9,246
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	£1,078	0.5171	£287	-0.0121	dominated	0.0%	£9,264
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,091	0.5162	£300	-0.0130	dominated	0.0%	£9,232
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,173	0.5131	£383	-0.0160	dominated	1.8%	£9,089
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,188	0.5131	£397	-0.0160	dominated	0.0%	£9,074
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,189	0.5136	£398	-0.0155	dominated	0.8%	£9,083
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,203	0.5136	£412	-0.0156	dominated	0.0%	£9,068
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,265	0.5226	£474	-0.0065	dominated	0.0%	£9,187
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,270	0.5225	£479	-0.0066	dominated	0.0%	£9,180

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	£1,282	0.5166	£491	-0.0125	dominated	1.0%	£9,050
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,297	0.5151	£506	-0.0140	dominated	0.5%	£9,005
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,304	0.5154	£513	-0.0137	dominated	0.0%	£9,005
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,311	0.5151	£520	-0.0141	dominated	0.0%	£8,990
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,318	0.5154	£527	-0.0138	dominated	0.0%	£8,990
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	£1,430	0.5188	£639	-0.0103	dominated	0.1%	£8,947
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	£1,439	0.5186	£648	-0.0105	dominated	0.2%	£8,934
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	£1,470	0.5141	£679	-0.0150	dominated	0.0%	£8,813
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,517	0.5128	£726	-0.0164	dominated	0.0%	£8,738
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,527	0.5122	£736	-0.0169	dominated	0.0%	£8,718
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,533	0.5127	£742	-0.0164	dominated	0.0%	£8,722
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,543	0.5122	£752	-0.0169	dominated	0.0%	£8,701
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	£1,609	0.5216	£818	-0.0075	dominated	0.0%	£8,823
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	£1,621	0.5215	£830	-0.0076	dominated	0.2%	£8,809
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	£1,918	0.5176	£1,127	-0.0116	dominated	0.0%	£8,434
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	£1,932	0.5174	£1,141	-0.0118	dominated	0.0%	£8,416

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 38: Cost-effectiveness acceptability curve for proctosigmoiditis and left-sided disease base-case analysis

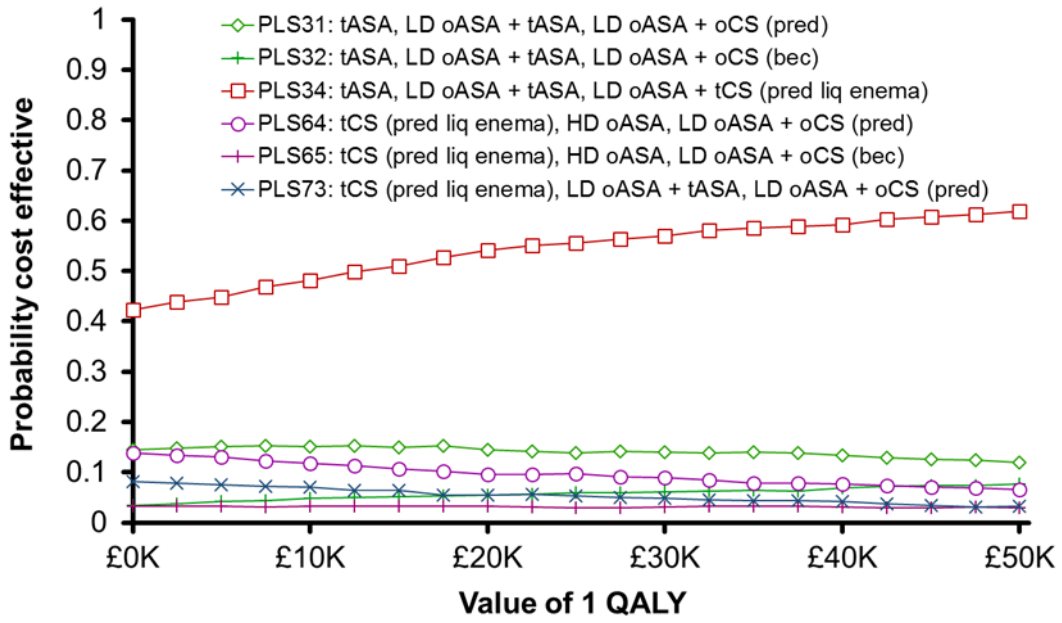
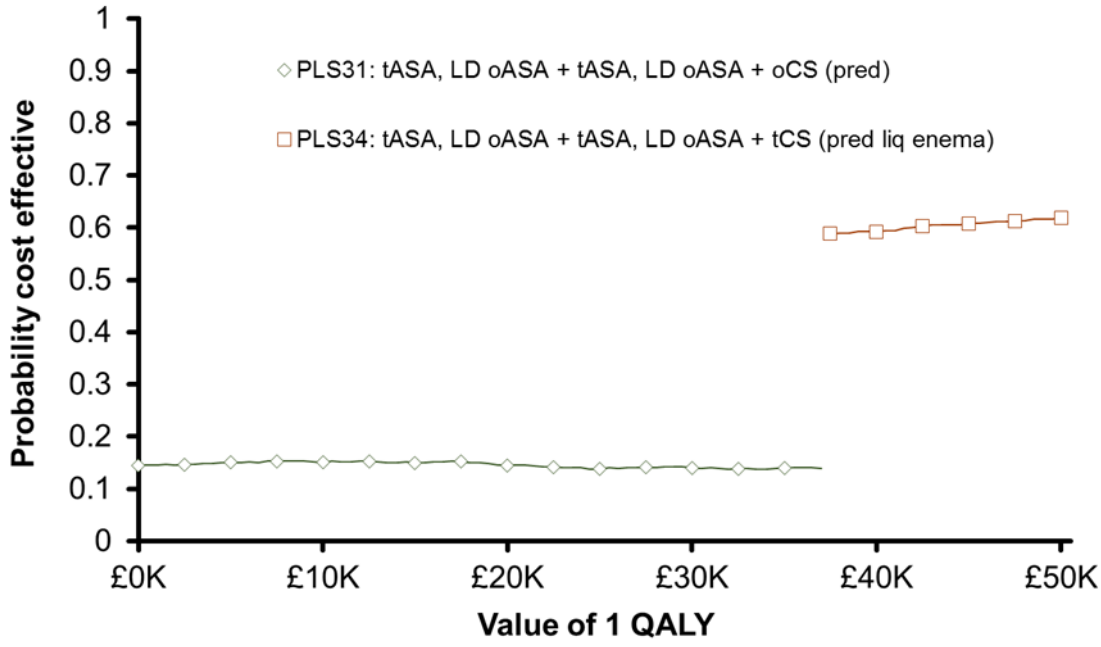


Figure 39: Cost-effectiveness acceptability frontier for proctosigmoiditis and left-sided disease base-case analysis



L.3.1.13 Scenario analyses

The incremental cost-effectiveness results, CEACs and CEAFs for various scenario analyses for proctosigmoiditis and left-sided disease are presented below.

SA1: Duration of treatment set to maximum of all RCTs for each drug

In this scenario analysis, the duration for each treatment is set to the maximum duration of follow-up reported in RCTs for each drug and allows for sequences containing topical hydrocortisone or topical budesonide to be compared using data from RCTs with a follow-up duration of 8 weeks. Estimates of the relative effectiveness of topical hydrocortisone, topical budesonide and topical aminosalicylates are derived from the evidence network at 5-8 weeks whereas topical prednisolone remains informed by the evidence network at 0-4 weeks. This results in sequences beginning with topical prednisolone generating higher QALYs and lower costs.

The CEAC in Figure 40 shows that PLS64, which begins with topical prednisolone, followed by a high-dose oral aminosalicylate and then a low-dose oral aminosalicylate in combination with an oral corticosteroid, is the most cost-effective strategy across the full range of threshold values but this result is associated with considerable uncertainty because 3 other strategies that begin with topical prednisolone (PLS73, PLS65, PLS74) all have approximately a 20% probability of being the most cost-effective strategy.

Table 70: SA1 cost-effectiveness results for proctosigmoiditis and left-sided disease with duration of treatment set to maximum of all RCTs for each drug

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	£830	0.5276				24.1%	£9,723
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	£834	0.5278	£4	0.0002	£25,503	19.6%	£9,722
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (becl)	£844	0.5276	£10	-0.0002	dominated	19.6%	£9,708
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (becl)	£847	0.5278	£13	0.0000	dominated	18.7%	£9,709
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	£852	0.5274	£18	-0.0004	dominated	2.7%	£9,697
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (becl)	£868	0.5274	£34	-0.0004	dominated	1.0%	£9,680
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	£957	0.5264	£123	-0.0014	dominated	0.1%	£9,570
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	£963	0.5261	£129	-0.0017	dominated	0.0%	£9,558
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£995	0.5194	£161	-0.0084	dominated	0.7%	£9,392

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	£999	0.5257	£165	-0.0021	dominated	0.0%	£9,514
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,043	0.5161	£209	-0.0118	dominated	0.0%	£9,278
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,057	0.5160	£223	-0.0118	dominated	0.0%	£9,264
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	£1,062	0.5174	£228	-0.0104	dominated	0.0%	£9,285
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,069	0.5163	£235	-0.0115	dominated	0.0%	£9,258
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	£1,076	0.5173	£242	-0.0105	dominated	0.0%	£9,271
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,082	0.5163	£248	-0.0115	dominated	0.0%	£9,244
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,156	0.5189	£322	-0.0089	dominated	3.3%	£9,222
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,171	0.5189	£337	-0.0089	dominated	3.4%	£9,206
PLS58	tCS (hydro), HD oASA, LD oASA + oCS (pred)	£1,190	0.5164	£356	-0.0114	dominated	1.1%	£9,138
PLS67	tCS (hydro), LD oASA + tASA, LD oASA + oCS (pred)	£1,196	0.5167	£362	-0.0111	dominated	1.6%	£9,139
PLS59	tCS (hydro), HD oASA, LD oASA + oCS (beclo)	£1,213	0.5164	£379	-0.0114	dominated	1.6%	£9,115
PLS68	tCS (hydro), LD oASA + tASA, LD oASA + oCS (bec)	£1,217	0.5167	£383	-0.0111	dominated	1.1%	£9,118
PLS49	tCS (hydro), LD oASA, LD oASA + oCS (pred)	£1,229	0.5160	£395	-0.0118	dominated	0.5%	£9,092
PLS35	tASA, LD oASA + tASA, LD oASA + tCS (hydro)	£1,232	0.5171	£398	-0.0107	dominated	0.3%	£9,111
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,253	0.5226	£419	-0.0052	dominated	0.0%	£9,200
PLS50	tCS (hydro), LD oASA, LD oASA + oCS (beclo)	£1,254	0.5160	£419	-0.0118	dominated	0.0%	£9,066
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,255	0.5226	£421	-0.0052	dominated	0.0%	£9,197
PLS36	tASA, LD oASA + tASA, LD oASA + tCS (bude)	£1,258	0.5172	£424	-0.0107	dominated	0.1%	£9,085
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	£1,280	0.5168	£446	-0.0111	dominated	0.1%	£9,055

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,281	0.5153	£447	-0.0125	dominated	0.1%	£9,026
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,287	0.5157	£453	-0.0121	dominated	0.1%	£9,027
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,296	0.5153	£462	-0.0125	dominated	0.0%	£9,011
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,302	0.5156	£468	-0.0122	dominated	0.0%	£9,011
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,304	0.5153	£470	-0.0125	dominated	0.0%	£9,002
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,307	0.5156	£473	-0.0122	dominated	0.0%	£9,005
PLS61	tCS (bud), HD oASA, LD oASA + oCS (pred)	£1,308	0.5166	£473	-0.0112	dominated	0.1%	£9,025
PLS70	tCS (bud), LD oASA + tASA, LD oASA + oCS (pred)	£1,313	0.5169	£479	-0.0109	dominated	0.0%	£9,026
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,319	0.5153	£485	-0.0125	dominated	0.0%	£8,987
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,322	0.5156	£488	-0.0122	dominated	0.0%	£8,990
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,328	0.5169	£494	-0.0109	dominated	0.0%	£9,009
PLS62	tCS (bud), HD oASA, LD oASA + oCS (beclo)	£1,329	0.5166	£495	-0.0112	dominated	0.0%	£9,003
PLS71	tCS (bud), LD oASA + tASA, LD oASA + oCS (beclo)	£1,332	0.5169	£498	-0.0109	dominated	0.0%	£9,006
PLS52	tCS (bud), LD oASA, LD oASA + oCS (pred)	£1,345	0.5162	£511	-0.0116	dominated	0.0%	£8,980
PLS29	HD oASA, LD oASA + tASA, LD oASA+ tCS (hydro)	£1,353	0.5146	£519	-0.0132	dominated	0.0%	£8,939
PLS53	tCS (bud), LD oASA, LD oASA + oCS (beclo)	£1,368	0.5162	£534	-0.0116	dominated	0.0%	£8,956
PLS30	HD oASA, LD oASA + tASA, LD oASA+ tCS (bude)	£1,384	0.5146	£550	-0.0132	dominated	0.0%	£8,909
PLS23	LD oASA, LD oASA + tASA, tCS (hydro)	£1,388	0.5133	£554	-0.0145	dominated	0.0%	£8,877
PLS11	LD oASA, HD oASA, LD oASA + tCS (hydro)	£1,391	0.5127	£557	-0.0151	dominated	0.0%	£8,864
PLS20	LD oASA, LD oASA + tASA, tCS (hydro)	£1,404	0.5132	£569	-0.0146	dominated	0.0%	£8,861

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS08	LD oASA, HD oASA, LD oASA + tCS (hydro)	£1,407	0.5127	£572	-0.0151	dominated	0.0%	£8,848
PLS69	tCS (hydro), LD oASA + tASA, LD oASA + oCS (bude)	£1,413	0.5142	£578	-0.0136	dominated	0.0%	£8,871
PLS24	LD oASA, LD oASA + tASA, tCS (bude)	£1,422	0.5133	£588	-0.0145	dominated	0.0%	£8,844
PLS60	PLS60: tCS (hydro), HD oASA, LD oASA + oCS (bude)	£1,426	0.5136	£592	-0.0142	dominated	0.0%	£8,846
PLS12	LD oASA, HD oASA, LD oASA + tCS (bude)	£1,428	0.5128	£594	-0.0150	dominated	0.0%	£8,828
PLS21	LD oASA, LD oASA + tASA, tCS (bud)	£1,438	0.5133	£604	-0.0145	dominated	0.0%	£8,827
PLS09	LD oASA, HD oASA, LD oASA + tCS (bude)	£1,444	0.5127	£609	-0.0151	dominated	0.0%	£8,811
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	£1,471	0.5143	£637	-0.0135	dominated	0.0%	£8,814
PLS51	tCS (hydro), LD oASA, LD oASA + oCS (bude)	£1,489	0.5129	£655	-0.0149	dominated	0.0%	£8,770
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,519	0.5129	£685	-0.0149	dominated	0.0%	£8,739
PLS72	tCS (bud), LD oASA + tASA, LD oASA + oCS (bude)	£1,526	0.5144	£692	-0.0134	dominated	0.0%	£8,762
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,532	0.5123	£698	-0.0155	dominated	0.0%	£8,714
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,535	0.5129	£701	-0.0150	dominated	0.0%	£8,722
PLS63	tCS (bud), HD oASA, LD oASA + oCS (bude)	£1,539	0.5139	£705	-0.0140	dominated	0.0%	£8,738
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,549	0.5123	£715	-0.0155	dominated	0.0%	£8,697
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	£1,579	0.5217	£745	-0.0061	dominated	0.1%	£8,854
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	£1,582	0.5216	£748	-0.0062	dominated	0.0%	£8,850
PLS54	tCS (bude), LD oASA, LD oASA + oCS (bude)	£1,600	0.5132	£766	-0.0146	dominated	0.0%	£8,663
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	£1,611	0.5216	£777	-0.0062	dominated	0.0%	£8,822
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	£1,615	0.5216	£781	-0.0062	dominated	0.0%	£8,817
PLS41	LD oASA + tASA, LD oASA + tCS (hydro)	£1,731	0.5181	£897	-0.0097	dominated	0.0%	£8,631
PLS47	LD oASA + tASA, LD oASA + tCS (hydro)	£1,735	0.5180	£901	-0.0098	dominated	0.0%	£8,626

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS42	LD oASA + tASA, LD oASA + tCS (bude)	£1,782	0.5181	£948	-0.0097	dominated	0.0%	£8,581
PLS48	LD oASA + tASA, LD oASA + tCS (hydro)	£1,786	0.5181	£952	-0.0097	dominated	0.0%	£8,575
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	£1,926	0.5175	£1,092	-0.0103	dominated	0.0%	£8,424
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	£1,932	0.5175	£1,097	-0.0103	dominated	0.0%	£8,418

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 40: SA1 cost-effectiveness acceptability curve for proctosigmoiditis and left-sided disease with duration of treatment set to maximum of all RCTs for each drug

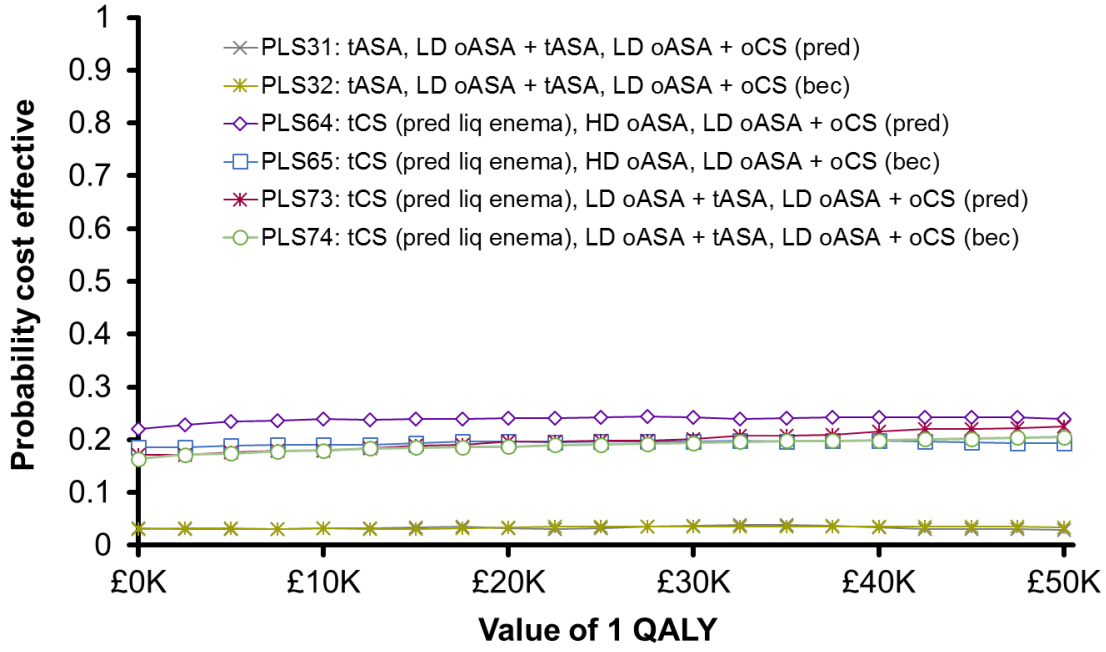
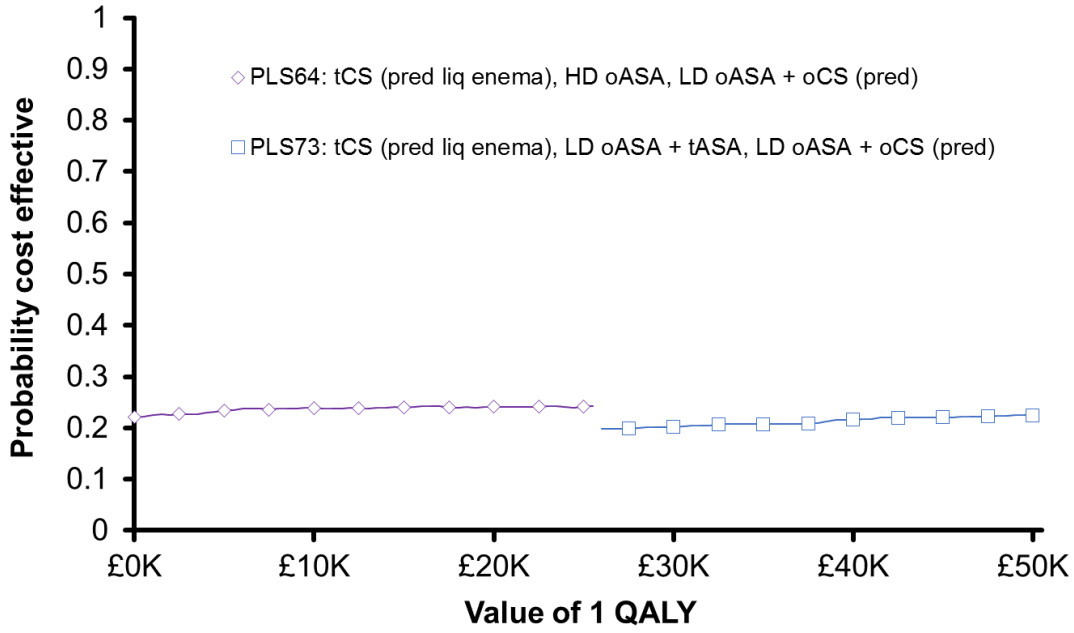


Figure 41: SA1 cost-effectiveness acceptability frontier for proctosigmoiditis and left-sided disease with duration of treatment set to maximum of all RCTs for each drug



SA2: No early switching of treatments in the event of non-remission

This scenario analysis assumes there is no early assessment of response to treatment. All people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome is remission or non-remission. Compared to the base case, there is an increase in costs for all sequences in this scenario analysis but sequences that start with a topical aminosalicylate still dominate. Table 71 shows that although PLS34 is associated with a higher probability of being the most cost-effective option at a threshold value of £20,000/QALY, PLS31 and PLS34 produce the same expected net monetary benefit. This is also reflected in Figure 43 where the frontier swtiches from PLS31 to PLS34 at £20,000/QALY.

Table 71: SA2 cost-effectiveness results for proctosigmoiditis and left-sided disease with no early switching of treatments in the event of non-remission

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£820	0.5238				12.5%	£9,656
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£846	0.5251	£26	0.0013	£20,340	55.6%	£9,656
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	£850	0.5199	£4	-0.0052	dominated	8.7%	£9,547

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£859	0.5249	£13	-0.0002	dominated	4.9%	£9,639
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	£864	0.5191	£18	-0.0060	dominated	1.2%	£9,518
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	£877	0.5204	£31	-0.0047	dominated	6.4%	£9,530
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (beclo)	£907	0.5214	£61	-0.0037	dominated	3.1%	£9,522
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (beclo)	£925	0.5208	£79	-0.0043	dominated	0.2%	£9,490
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (beclo)	£929	0.5218	£83	-0.0032	dominated	1.9%	£9,508
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£957	0.5230	£111	-0.0021	dominated	0.0%	£9,504
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	£1,051	0.5187	£205	-0.0064	dominated	0.0%	£9,324
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	£1,061	0.5193	£215	-0.0058	dominated	0.0%	£9,325
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	£1,086	0.5178	£240	-0.0073	dominated	0.0%	£9,270
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,136	0.5020	£290	-0.0231	dominated	0.0%	£8,903
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,173	0.5019	£327	-0.0232	dominated	0.0%	£8,865
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,185	0.5025	£339	-0.0225	dominated	0.0%	£8,866
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	£1,189	0.5048	£343	-0.0203	dominated	0.0%	£8,907
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	£1,205	0.5044	£359	-0.0207	dominated	0.0%	£8,882
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,222	0.5025	£376	-0.0226	dominated	0.0%	£8,827
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,279	0.4977	£432	-0.0274	dominated	2.4%	£8,675
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,317	0.4975	£471	-0.0276	dominated	0.0%	£8,634
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,318	0.4985	£472	-0.0265	dominated	0.8%	£8,653
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,356	0.4984	£510	-0.0267	dominated	0.0%	£8,612

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,374	0.5004	£528	-0.0247	dominated	0.6%	£8,634
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,381	0.5145	£535	-0.0106	dominated	0.0%	£8,909
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,392	0.5140	£546	-0.0111	dominated	0.0%	£8,888
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	£1,398	0.5038	£552	-0.0213	dominated	1.3%	£8,677
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,404	0.5011	£558	-0.0240	dominated	0.2%	£8,618
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,412	0.5003	£566	-0.0248	dominated	0.0%	£8,593
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,442	0.5010	£596	-0.0241	dominated	0.0%	£8,577
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	£1,569	0.5088	£723	-0.0163	dominated	0.0%	£8,607
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	£1,588	0.5082	£742	-0.0169	dominated	0.1%	£8,575
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	£1,616	0.4994	£770	-0.0256	dominated	0.1%	£8,372
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,642	0.4956	£796	-0.0295	dominated	0.0%	£8,270
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,654	0.4966	£808	-0.0285	dominated	0.0%	£8,278
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,684	0.4954	£838	-0.0297	dominated	0.0%	£8,224
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,696	0.4964	£850	-0.0286	dominated	0.0%	£8,233
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	£1,705	0.5128	£859	-0.0123	dominated	0.0%	£8,551
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	£1,729	0.5123	£883	-0.0128	dominated	0.0%	£8,517
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	£2,049	0.5060	£1,203	-0.0191	dominated	0.0%	£8,071
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	£2,079	0.5053	£1,233	-0.0198	dominated	0.0%	£8,028

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 42: SA2 cost-effectiveness acceptability curve for proctosigmoiditis and left-sided disease with no early switching of treatments in the event of non-remission

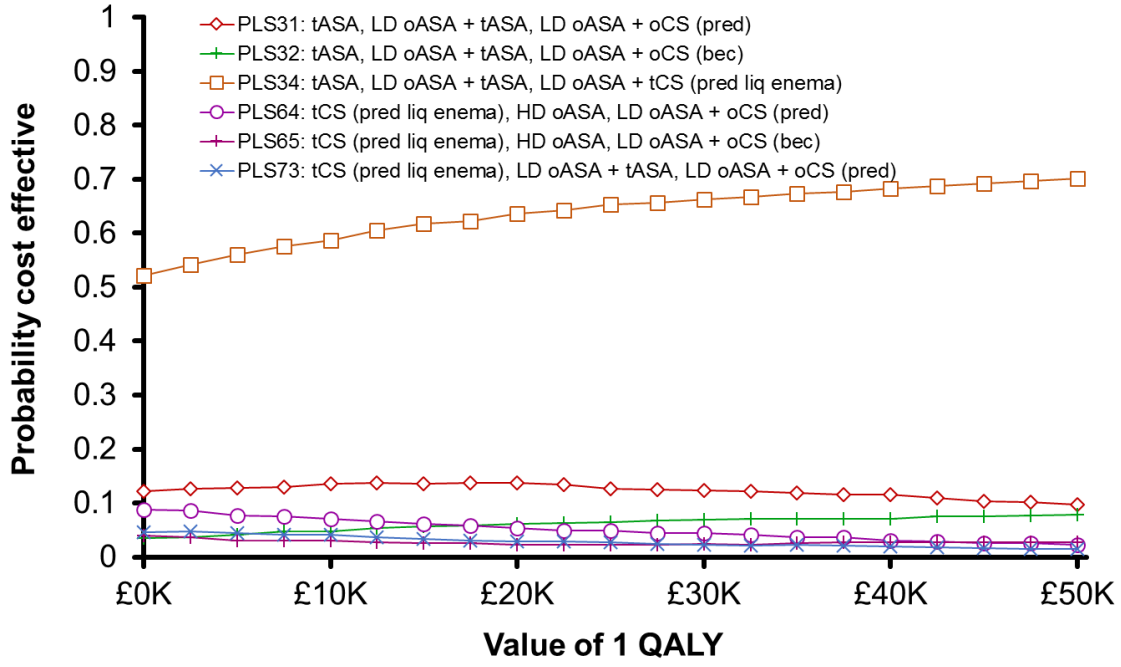
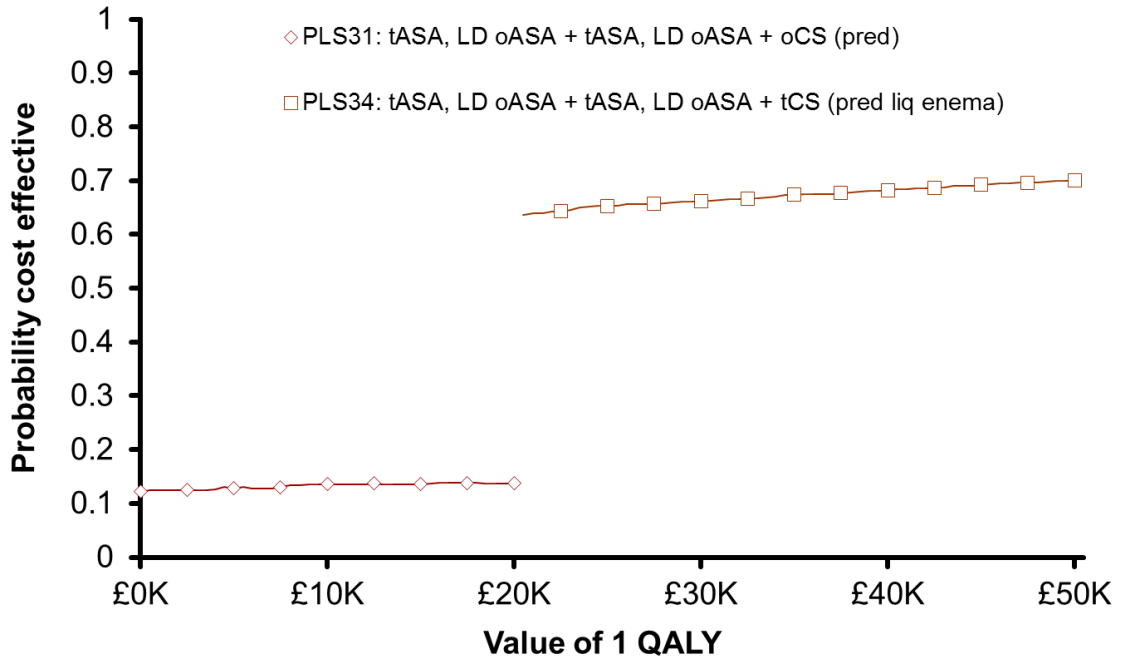


Figure 43: SA2 cost-effectiveness acceptability frontier for proctosigmoiditis and left-sided disease with no early switching of treatments in the event of non-remission



SA3: Duration of maintenance on biological therapies

This scenario analysis was run for each extent of disease and assumed that people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model.

There is an increase in costs for all sequences in this scenario analysis compared to the base-case analysis but sequences that start with a topical aminosalicylate still dominate. Figure 44 and Figure 45 show that at a threshold value of £20,000/QALY, PLS31 produces the highest expected net benefit even though PLS34 has a higher probability of being the most cost-effective option. Once again, this is due to asymmetry in the distributions of expected value as previously noted in the results for the base-case analysis.

Table 72: SA3 cost-effectiveness results for proctosigmoiditis and left-sided disease assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£770	0.5285				13.7%	£9,799
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£803	0.5293	£32	0.0008	£39,038	63.6%	£9,783
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	£797	0.5265	£26	-0.0019	dominated	5.3%	£9,734
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£822	0.5292	£20	-0.0001	dominated	6.1%	£9,762
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	£815	0.5262	£12	-0.0031	dominated	0.4%	£9,709
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	£806	0.5268	£3	-0.0025	dominated	2.9%	£9,729
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (beclo)	£866	0.5276	£64	-0.0017	dominated	2.3%	£9,685
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (beclo)	£891	0.5273	£88	-0.0020	dominated	0.2%	£9,656
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (beclo)	£873	0.5277	£70	-0.0016	dominated	1.0%	£9,682
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£903	0.5281	£100	-0.0012	dominated	0.0%	£9,660
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	£982	0.5261	£179	-0.0032	dominated	0.0%	£9,539
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	£979	0.5263	£176	-0.0030	dominated	0.0%	£9,548
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	£1,020	0.5257	£217	-0.0036	dominated	0.0%	£9,494

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,059	0.5161	£257	-0.0132	dominated	0.0%	£9,262
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,073	0.5160	£270	-0.0133	dominated	0.0%	£9,248
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	£1,080	0.5173	£278	-0.0120	dominated	0.0%	£9,266
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	£1,089	0.5172	£286	-0.0121	dominated	0.0%	£9,255
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,089	0.5163	£286	-0.0130	dominated	0.0%	£9,237
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,103	0.5163	£300	-0.0130	dominated	0.0%	£9,223
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,202	0.5132	£400	-0.0161	dominated	1.7%	£9,062
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,217	0.5132	£414	-0.0161	dominated	0.0%	£9,047
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,219	0.5137	£416	-0.0156	dominated	0.1%	£9,054
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,233	0.5136	£431	-0.0157	dominated	0.0%	£9,039
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,332	0.5152	£529	-0.0141	dominated	0.6%	£8,972
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,346	0.5152	£544	-0.0141	dominated	0.0%	£8,957
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	£1,306	0.5227	£503	-0.0066	dominated	0.0%	£9,148
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,311	0.5226	£509	-0.0067	dominated	0.0%	£9,140
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,316	0.5167	£513	-0.0126	dominated	1.0%	£9,017
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,341	0.5155	£539	-0.0138	dominated	0.0%	£8,968
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,356	0.5155	£553	-0.0138	dominated	0.0%	£8,953
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	£1,497	0.5142	£695	-0.0151	dominated	0.0%	£8,786
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	£1,505	0.5188	£702	-0.0105	dominated	0.7%	£8,871
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	£1,515	0.5186	£712	-0.0107	dominated	0.3%	£8,858

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,547	0.5128	£745	-0.0165	dominated	0.0%	£8,709
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,555	0.5123	£753	-0.0170	dominated	0.0%	£8,691
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,564	0.5128	£761	-0.0165	dominated	0.0%	£8,693
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,572	0.5123	£769	-0.0170	dominated	0.0%	£8,674
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	£1,703	0.5216	£900	-0.0077	dominated	0.0%	£8,730
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	£1,716	0.5215	£913	-0.0078	dominated	0.1%	£8,714
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	£2,010	0.5176	£1,207	-0.0117	dominated	0.0%	£8,341
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	£2,025	0.5174	£1,223	-0.0119	dominated	0.0%	£8,322

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 44: SA3 cost-effectiveness acceptability curve for proctosigmoiditis and left-sided disease assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model

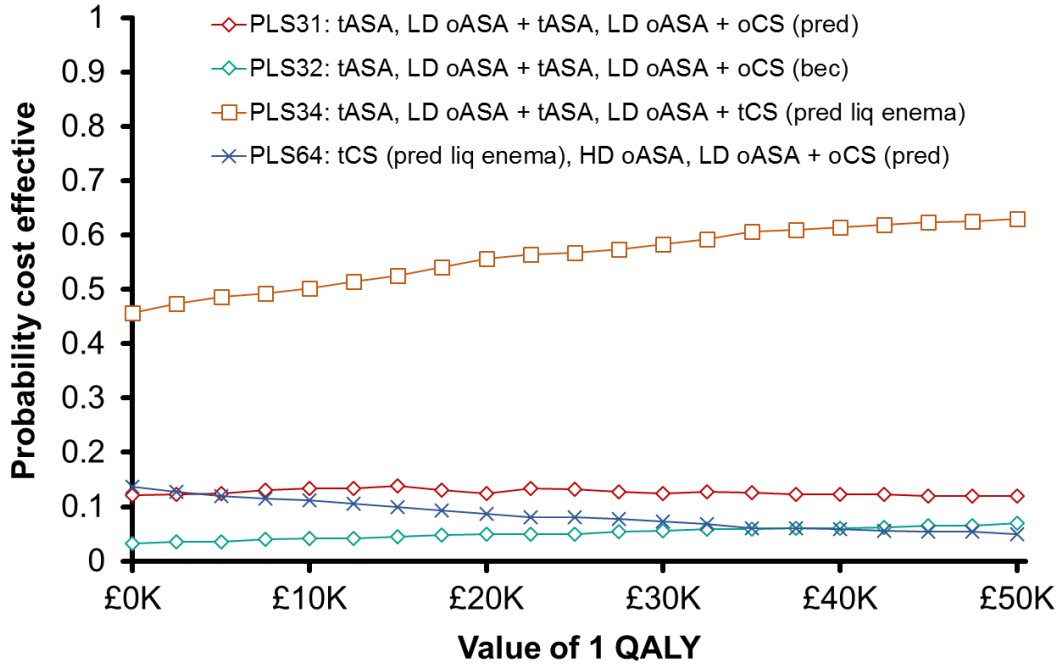
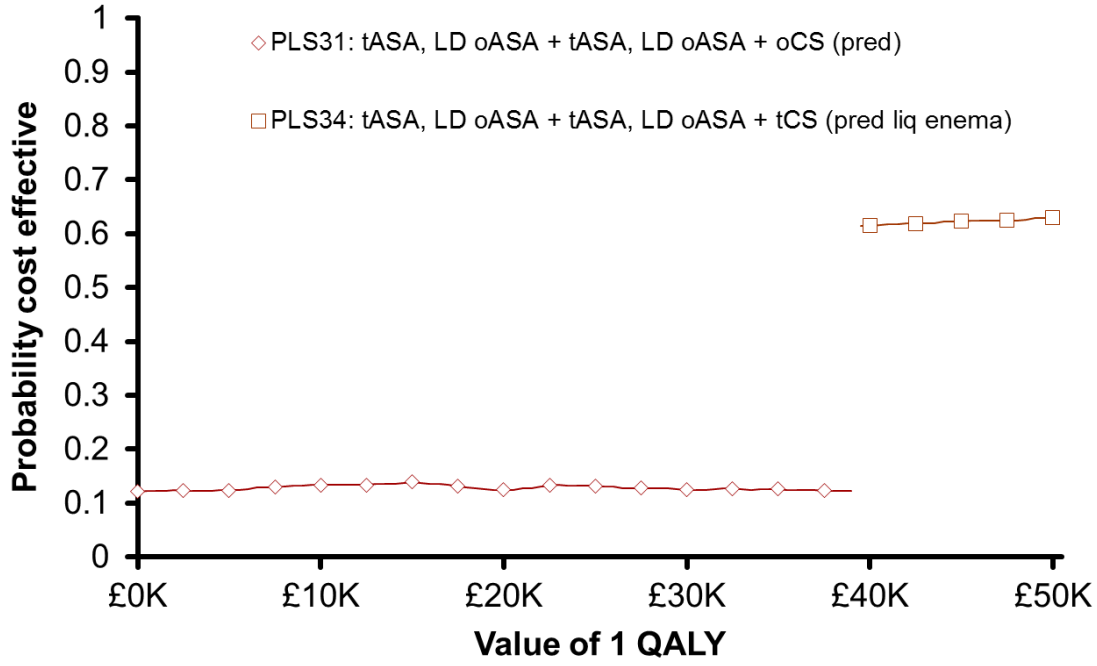


Figure 45: SA3 cost-effectiveness acceptability frontier for proctosigmoiditis and left-sided disease assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model



SA4: Vary drug price for topical prednisolone

Two different preparations of topical prednisolone are available and costs vary considerably. A scenario analysis was run in proctosigmoiditis and left-sided disease varying the price of topical prednisolone from £7.50 (liquid enema) to £93.50 (foam enema).

The cost of sequences containing topical prednisolone increase but sequences that start with a topical aminosalicylate still dominate. With the increase in cost of topical prednisolone as third-line treatment in PLS34, PLS31 now produces the highest expected net benefit up to a threshold value of £37,000/QALY as shown in Figure 47.

Table 73: SA4 cost-effectiveness results for proctosigmoiditis and left-sided disease varying the cost of topical prednisolone

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS31	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£760	0.5283				12.5%	£9,806
PLS64	tCS (pred liq enema), HD oASA, LD oASA + oCS (pred)	£785	0.5263	£25	-0.0020	dominated	8.7%	£9,740
PLS34	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£791	0.5291	£31	0.0008	£37,349	55.6%	£9,792
PLS73	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (pred)	£794	0.5265	£3	-0.0026	dominated	6.4%	£9,737

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS55	tCS (pred liq enema), LD oASA, LD oASA + oCS (pred)	£801	0.5259	£10	-0.0032	dominated	1.2%	£9,718
PLS32	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£809	0.5291	£18	-0.0001	dominated	4.9%	£9,772
PLS65	tCS (pred liq enema), HD oASA, LD oASA + oCS (beclo)	£853	0.5273	£62	-0.0018	dominated	3.1%	£9,694
PLS74	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (beclo)	£858	0.5275	£67	-0.0016	dominated	1.9%	£9,693
PLS56	tCS (pred liq enema), LD oASA, LD oASA + oCS (beclo)	£875	0.5271	£84	-0.0021	dominated	0.2%	£9,667
PLS33	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£894	0.5280	£103	-0.0012	dominated	0.0%	£9,665
PLS75	tCS (pred liq enema), LD oASA + tASA, LD oASA + oCS (bude)	£969	0.5261	£178	-0.0030	dominated	0.0%	£9,553
PLS66	tCS (pred liq enema), HD oASA, LD oASA + oCS (bude)	£975	0.5258	£185	-0.0033	dominated	0.0%	£9,540
PLS57	tCS (pred liq enema), LD oASA, LD oASA + oCS (bude)	£1,011	0.5254	£220	-0.0037	dominated	0.0%	£9,497
PLS10	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,050	0.5159	£259	-0.0132	dominated	0.0%	£9,268
PLS07	LD oASA, HD oASA, LD oASA + tCS (pred liq enema)	£1,064	0.5159	£273	-0.0132	dominated	0.0%	£9,254
PLS28	HD oASA, LD oASA + tASA, LD oASA+ tCS (pred liq enema)	£1,071	0.5172	£280	-0.0119	dominated	0.0%	£9,274
PLS22	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,077	0.5162	£286	-0.0130	dominated	0.0%	£9,246
PLS25	HD oASA, LD oASA + tASA, LD oASA+ oCS (pred)	£1,078	0.5171	£287	-0.0121	dominated	0.0%	£9,264
PLS19	LD oASA, LD oASA + tASA, tCS (pred liq enema)	£1,091	0.5162	£300	-0.0130	dominated	0.0%	£9,232
PLS04	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,173	0.5131	£383	-0.0160	dominated	2.4%	£9,089
PLS01	LD oASA, HD oASA, LD oASA + oCS (pred)	£1,188	0.5131	£397	-0.0160	dominated	0.0%	£9,074
PLS16	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,189	0.5136	£398	-0.0155	dominated	0.8%	£9,083
PLS13	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,203	0.5136	£412	-0.0156	dominated	0.0%	£9,068
PLS40	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,265	0.5226	£474	-0.0065	dominated	0.0%	£9,187

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PLS46	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,270	0.5225	£479	-0.0066	dominated	0.0%	£9,180
PLS26	HD oASA, LD oASA + tASA, LD oASA+ oCS (beclo)	£1,282	0.5166	£491	-0.0125	dominated	1.3%	£9,050
PLS05	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,297	0.5151	£506	-0.0140	dominated	0.6%	£9,005
PLS17	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,304	0.5154	£513	-0.0137	dominated	0.2%	£9,005
PLS02	LD oASA, HD oASA, LD oASA + oCS (beclo)	£1,311	0.5151	£520	-0.0141	dominated	0.0%	£8,990
PLS14	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£1,318	0.5154	£527	-0.0138	dominated	0.0%	£8,990
PLS37	LD oASA + tASA, LD oASA + oCS (pred)	£1,430	0.5188	£639	-0.0103	dominated	0.0%	£8,947
PLS43	LD oASA + tASA, LD oASA + oCS (pred)	£1,439	0.5186	£648	-0.0105	dominated	0.1%	£8,934
PLS27	HD oASA, LD oASA + tASA, LD oASA+ oCS (bude)	£1,470	0.5141	£679	-0.0150	dominated	0.1%	£8,813
PLS18	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,517	0.5128	£726	-0.0164	dominated	0.0%	£8,738
PLS06	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,527	0.5122	£736	-0.0169	dominated	0.0%	£8,718
PLS15	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,533	0.5127	£742	-0.0164	dominated	0.0%	£8,722
PLS03	LD oASA, HD oASA, LD oASA + oCS (bude)	£1,543	0.5122	£752	-0.0169	dominated	0.0%	£8,701
PLS38	LD oASA + tASA, LD oASA + oCS (beclo)	£1,609	0.5216	£818	-0.0075	dominated	0.0%	£8,823
PLS44	LD oASA + tASA, LD oASA + oCS (beclo)	£1,621	0.5215	£830	-0.0076	dominated	0.0%	£8,809
PLS39	LD oASA + tASA, LD oASA + oCS (bude)	£1,918	0.5176	£1,127	-0.0116	dominated	0.0%	£8,434
PLS45	LD oASA + tASA, LD oASA + oCS (bude)	£1,932	0.5174	£1,141	-0.0118	dominated	0.0%	£8,416

PLS = proctosigmoiditis and left-sided disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 46: SA4 cost-effectiveness acceptability curve for proctosigmoiditis and left-sided disease varying the cost of topical prednisolone

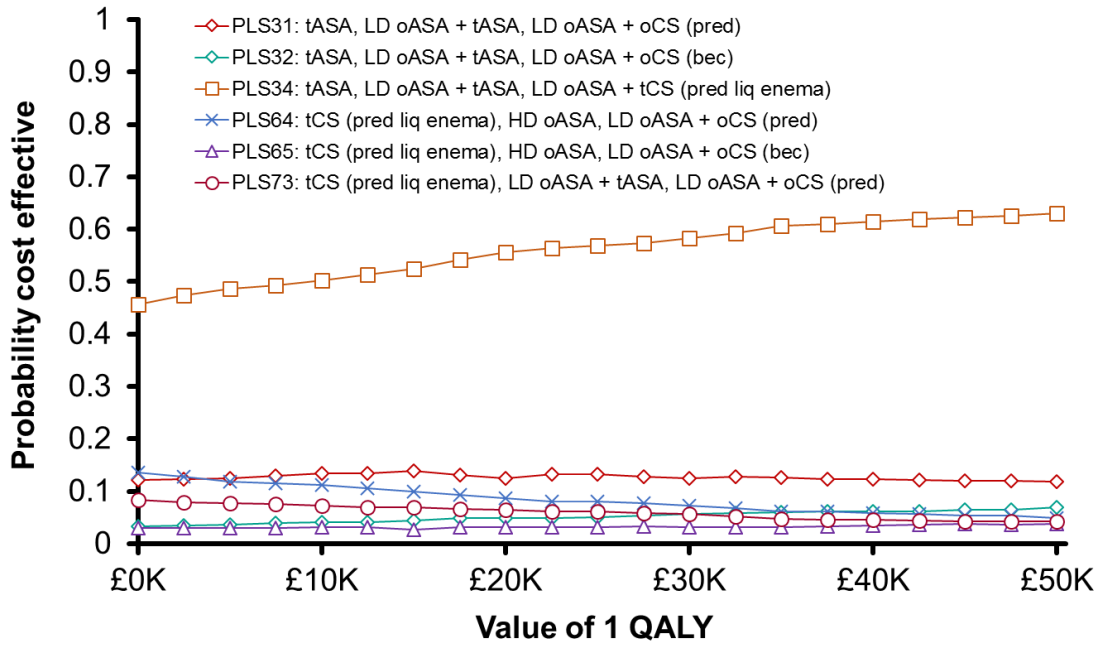
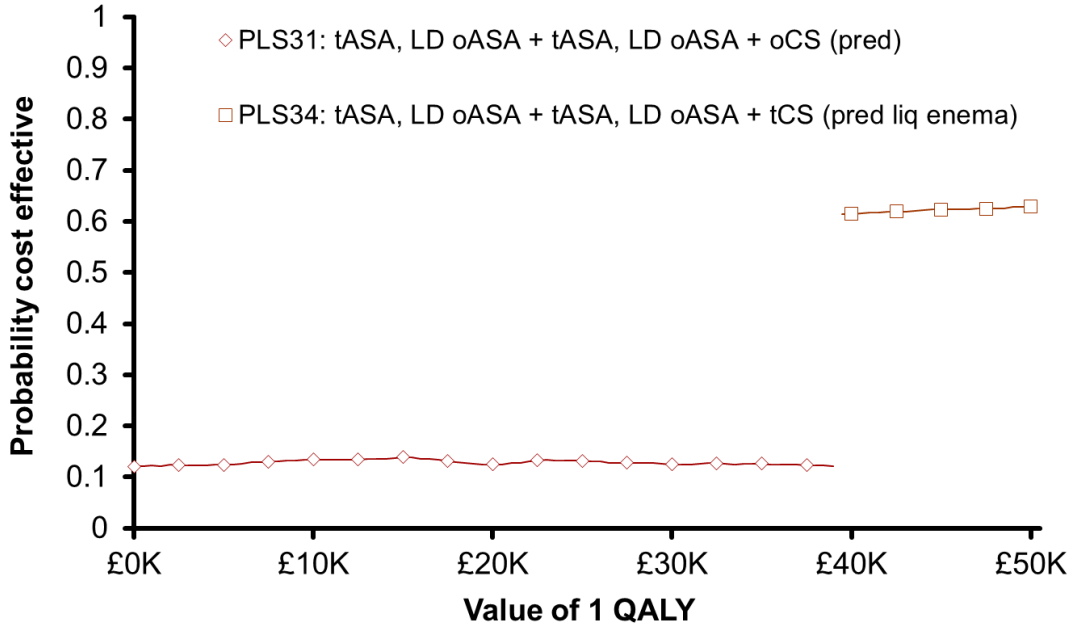


Figure 47: SA4 cost-effectiveness acceptability frontier for proctosigmoiditis and left-sided disease varying the cost of topical prednisolone



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L.3.12 Proctitis

In proctitis, RCT evidence was only available to estimate relative effectiveness of 3 active treatments: low-dose oral aminosalicylates, topical aminosalicylates and topical tacrolimus. In order to conduct a cost-effectiveness analysis of sequences of treatments of interest to the committee, it was necessary to assume that the estimates of relative effectiveness that were reported for other treatments in other extents of disease would also be applicable to proctitis.

L.3.28.1 Remission by line of treatment

Table 74 shows the proportion of people whose disease entered clinical remission in each line of treatment for each sequence in the base case analysis for proctitis. Sequences PRC17 – PRC32 are the same as sequences PRC01 – PRC16 but without topical tacrolimus as a fourth line treatment option. PRC09 – PRC12 and PRC13 – PRC16 appear identical in terms of the sequence of treatments if remission is not achieved but differ in terms of the treatment assumption in the event of withdrawal (see Table 50). The same explanation applies to PRC25 – PRC28 and PRC29 – PRC32.

Sequences that begin with topical aminosalicylate (PRC01 – PRC04), have the highest proportion of people entering remission in first line (90.5%) and the lowest proportion of people requiring rescue therapy (0.1% - 0.4%). For these sequences, people spend on average 2.5 – 2.7 weeks out of 30 weeks with active disease. In constrast, sequences that begin with low-dose oral aminosalicylate (PRC06 – PRC08), followed by escalation to high-dose oral aminosalicylate and then the addition of an oral corticosteroid, result in people spending on average more than twice the amount of time (7.9 – 8.1 weeks) with active disease.

Table 74 also shows the costs of each treatment sequence broken down into the following categories: cost of drugs for induction of remission, cost of rescue therapy, cost of other healthcare resource use (consultant, nurse, GP, outpatient appointments, A&E attendances and blood tests) and cost of maintenance treatment. As with the results for proctosigmoiditis and left-sided disease, the proportion of patients requiring rescue therapy accounts for the biggest differences in costs when comparing treatment sequences.. Where fewer lines of treatment have been modelled, the proportion of people requiring rescue therapy is higher; giving more lines treatment to induce remission even in a small proportion of people with active disease can offset the much higher costs of rescue therapy.

Table 74: Proportion of people whose disease enters remission by line of treatment, average time spent in active disease vs. remission and breakdown of costs for each treatment sequence in base case analysis for proctitis

Treatment sequence		Proportion entering remission					Weeks active	Weeks remiss	Costs				
		1st line	2nd line	3rd line	4th line	Rescue			Drug	Rescue	Other HC	Main	Tottal
PRC01	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	90.5%	4.8%	3.8%	0.8%	0.1%	2.5	27.5	£63	£4	£199	£155	£421
PRC02	tASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	90.5%	4.8%	2.6%	1.8%	0.3%	2.6	27.4	£65	£9	£202	£153	£429
PRC03	tASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	90.5%	4.8%	3.1%	1.4%	0.2%	2.5	27.5	£65	£7	£200	£154	£427
PRC04	tASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	90.5%	4.8%	1.6%	2.6%	0.4%	2.7	27.3	£69	£14	£203	£153	£439
PRC05	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	40.0%	32.1%	22.6%	4.5%	0.7%	7.0	23.0	£155	£24	£323	£119	£621
PRC06	LD oASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	40.0%	32.1%	15.4%	10.7%	1.8%	7.9	22.1	£165	£56	£337	£111	£669
PRC07	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	40.0%	32.1%	18.3%	8.3%	1.4%	7.2	22.8	£164	£43	£330	£117	£655
PRC08	LD oASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	40.0%	32.1%	9.7%	15.6%	2.6%	8.1	21.9	£192	£81	£346	£110	£730
PRC09	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	51.3%	39.6%	7.8%	0.0%	1.3%	5.3	24.7	£175	£40	£269	£131	£615
PRC10	LD oASA + tASA, LD oASA + oCS (pred), tTAC	51.3%	27.4%	18.3%	0.0%	3.0%	6.8	23.2	£191	£95	£293	£118	£697
PRC11	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	51.3%	32.2%	14.1%	0.0%	2.3%	5.6	24.4	£190	£73	£282	£129	£674
PRC12	LD oASA + tASA, LD oASA + oCS (bude), tTAC	51.3%	17.7%	26.5%	0.1%	4.4%	7.2	22.8	£237	£139	£309	£116	£801

Treatment sequence		Proportion entering remission					Weeks active	Weeks remiss	Costs				
		1st line	2nd line	3rd line	4th line	Rescue			Drug	Rescue	Other HC	Main	Tottal
PRC13	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	51.3%	39.0%	8.3%	0.1%	1.3%	5.4	24.6	£175	£41	£270	£131	£617
PRC14	LD oASA + tASA, LD oASA + oCS (pred), tTAC	51.3%	26.7%	18.6%	0.3%	3.1%	6.8	23.2	£192	£96	£295	£118	£700
PRC15	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	51.3%	31.6%	14.5%	0.3%	2.4%	5.7	24.3	£191	£75	£283	£128	£677
PRC16	LD oASA + tASA, LD oASA + oCS (bude), tTAC	51.3%	17.1%	26.8%	0.4%	4.5%	7.2	22.8	£238	£140	£311	£115	£805
PRC17	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	90.5%	4.8%	3.8%	0.0%	0.9%	2.5	27.5	£62	£28	£199	£155	£444
PRC18	tASA, LD oASA + tASA, LD oASA + oCS (pred)	90.5%	4.8%	2.6%	0.0%	2.1%	2.6	27.4	£62	£66	£201	£154	£483
PRC19	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	90.5%	4.8%	3.1%	0.0%	1.6%	2.5	27.5	£63	£51	£200	£155	£469
PRC20	tASA, LD oASA + tASA, LD oASA + oCS (bude)	90.5%	4.8%	1.6%	0.0%	3.0%	2.6	27.4	£65	£96	£202	£154	£518
PRC21	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	40.0%	32.1%	22.6%	0.0%	5.3%	6.9	23.1	£149	£167	£321	£121	£757
PRC22	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	40.0%	32.1%	15.4%	0.0%	12.5%	7.6	22.4	£150	£394	£332	£116	£992
PRC23	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	40.0%	32.1%	18.3%	0.0%	9.7%	7.0	23.0	£153	£304	£327	£121	£905
PRC24	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	40.0%	32.1%	9.7%	0.0%	18.2%	7.7	22.3	£170	£573	£340	£117	£1,200
PRC25	LD oASA + tASA, LD oASA + tCS (pred liq enema)	51.3%	39.6%	0.1%	0.0%	9.0%	5.1	24.9	£164	£284	£266	£134	£848
PRC26	LD oASA + tASA, LD oASA + oCS (pred)	51.3%	27.4%	0.1%	0.0%	21.3%	6.2	23.8	£165	£671	£286	£126	£1,247
PRC27	LD oASA + tASA, LD oASA + oCS (beclo)	51.3%	32.2%	0.1%	0.0%	16.4%	5.2	24.8	£170	£517	£276	£134	£1,098

Treatment sequence		Proportion entering remission					Weeks active	Weeks remiss	Costs				
		1st line	2nd line	3rd line	4th line	Rescue			Drug	Rescue	Other HC	Main	Tottal
PRC28	LD oASA + tASA, LD oASA + oCS (bude)	51.3%	17.7%	0.0%	0.0%	31.0%	6.4	23.6	£199	£976	£299	£127	£1,602
PRC29	LD oASA + tASA, LD oASA + tCS (pred liq enema)	51.3%	39.0%	0.6%	0.0%	9.1%	5.1	24.9	£164	£288	£267	£134	£853
PRC30	LD oASA + tASA, LD oASA + oCS (pred)	51.3%	26.7%	0.4%	0.0%	21.6%	6.3	23.7	£165	£680	£287	£125	£1,258
PRC31	LD oASA + tASA, LD oASA + oCS (beclo)	51.3%	31.6%	0.4%	0.0%	16.7%	5.3	24.7	£170	£526	£277	£134	£1,108
PRC32	LD oASA + tASA, LD oASA + oCS (bude)	51.3%	17.1%	0.3%	0.0%	31.4%	6.5	23.5	£200	£990	£300	£127	£1,617
Minimum		***40.0%***	***4.8%***	***0.0%***	***0.0%***	***0.1%***	***2.5***	***21.9***	***£62***	***£4***	***£199***	***£110***	***£421***
Maximum		***90.5%***	***39.6%***	***26.8%***	***15.6%***	***31.4%***	***8.1***	***27.5***	***£238***	***£990***	***£346***	***£155***	***£1,617***

PRC = proctitis; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; tTAC = topical tacrolimus; pred = prednisolone; beclo = beclometasone; bude = budesonide; remiss = remission; HC = healthcare; Main = maintenance

L.3.2.12 Cost-effectiveness results

Table 75 summarises the base-case cost-effectiveness results in proctitis with sequences ordered from least costly to most costly. Treatment sequences beginning with a topical aminosalicylate, followed by the addition of an oral aminosalicylate, then a topical or oral corticosteroid and then topical tacrolimus are expected to generate more QALYs and incur lower costs than all other treatment sequences.

The CEAC in Figure 48 shows all treatment sequences that have a >3% probability of being cost effective. Figure 49 confirms that PRC01 has the highest expected net benefit over the range of threshold values from £0/QALY to £50,000/QALY.

Table 75: Base-case cost-effectiveness results for proctitis

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC01	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£448	0.5318				72.5%	£10,188
PRC03	tASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£459	0.5316	£11	-0.0001	dominated	18.4%	£10,174
PRC02	tASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£463	0.5312	£15	-0.0006	dominated	4.2%	£10,160
PRC04	tASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£486	0.5309	£38	-0.0008	dominated	0.0%	£10,133
PRC17	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£486	0.5319	£38	0.0001	£313,594	3.9%	£10,152
PRC19	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£514	0.5318	£27	-0.0001	dominated	0.5%	£10,123
PRC18	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£529	0.5314	£43	-0.0005	dominated	0.5%	£10,098
PRC20	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£578	0.5312	£92	-0.0007	dominated	0.0%	£10,047
PRC05	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£669	0.5178	£183	-0.0141	dominated	0.0%	£9,687
PRC09	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£699	0.5229	£213	-0.0090	dominated	0.0%	£9,758
PRC13	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£702	0.5227	£216	-0.0092	dominated	0.0%	£9,752
PRC07	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£712	0.5173	£226	-0.0146	dominated	0.0%	£9,633
PRC06	LD oASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£730	0.5152	£244	-0.0167	dominated	0.0%	£9,575

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC11	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£769	0.5220	£283	-0.0099	dominated	0.0%	£9,671
PRC15	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£774	0.5218	£288	-0.0101	dominated	0.0%	£9,662
PRC10	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£800	0.5185	£314	-0.0134	dominated	0.0%	£9,570
PRC14	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£804	0.5183	£318	-0.0136	dominated	0.0%	£9,562
PRC08	LD oASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£818	0.5144	£332	-0.0175	dominated	0.0%	£9,470
PRC21	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£825	0.5183	£339	-0.0136	dominated	0.0%	£9,541
PRC23	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£935	0.5179	£449	-0.0140	dominated	0.0%	£9,424
PRC12	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£949	0.5171	£463	-0.0148	dominated	0.0%	£9,393
PRC16	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£956	0.5169	£469	-0.0150	dominated	0.0%	£9,382
PRC25	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£960	0.5236	£473	-0.0083	dominated	0.0%	£9,513
PRC29	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£966	0.5235	£480	-0.0084	dominated	0.0%	£9,504
PRC22	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,007	0.5160	£521	-0.0159	dominated	0.0%	£9,313
PRC27	LD oASA + tASA, LD oASA + oCS (beclo)	£1,141	0.5231	£655	-0.0088	dominated	0.0%	£9,322
PRC31	LD oASA + tASA, LD oASA + oCS (beclo)	£1,151	0.5229	£665	-0.0090	dominated	0.0%	£9,307
PRC24	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,203	0.5155	£717	-0.0164	dominated	0.0%	£9,107
PRC26	LD oASA + tASA, LD oASA + oCS (pred)	£1,264	0.5198	£778	-0.0121	dominated	0.0%	£9,132
PRC30	LD oASA + tASA, LD oASA + oCS (pred)	£1,275	0.5196	£789	-0.0123	dominated	0.0%	£9,117
PRC28	LD oASA + tASA, LD oASA + oCS (bude)	£1,597	0.5190	£1,111	-0.0129	dominated	0.0%	£8,782
PRC32	LD oASA + tASA, LD oASA + oCS (bude)	£1,613	0.5188	£1,127	-0.0131	dominated	0.0%	£8,763

PRC = proctitis; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; tTAC = topical tacrolimus; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) *Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space*

Figure 48: Cost-effectiveness acceptability curve for proctitis base-case analysis

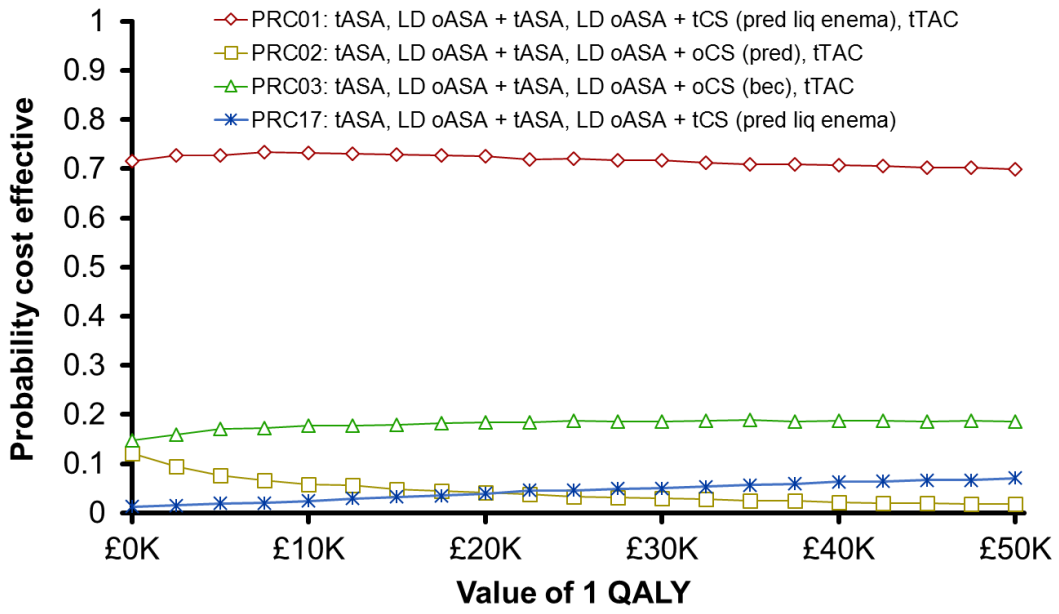

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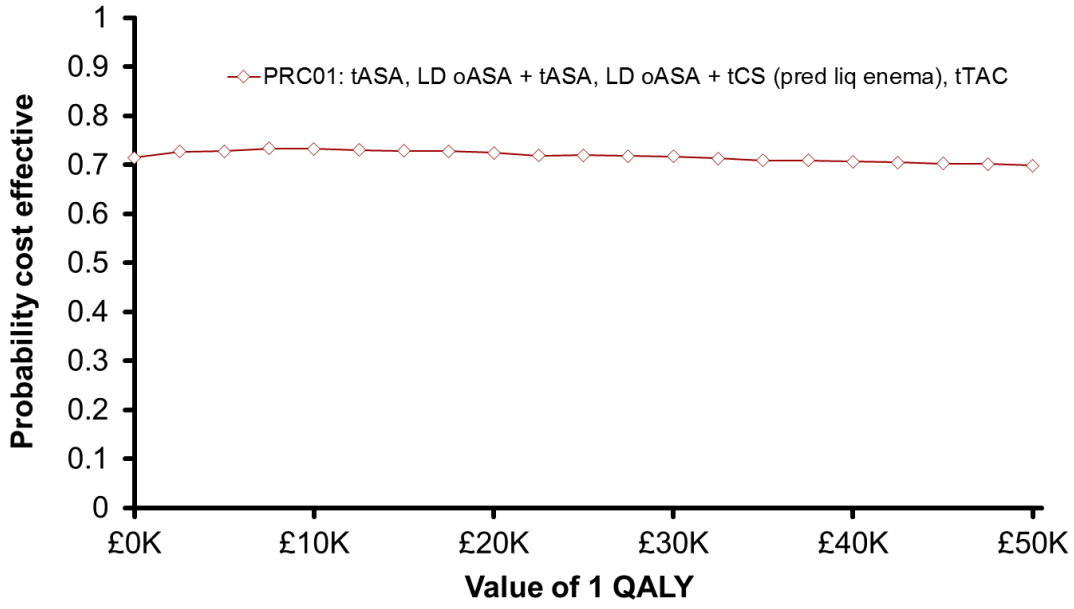
Figure 49: Cost-effectiveness acceptability frontier for proctitis base-case analysis



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L.3.233 Scenario analyses

4

5 The incremental cost-effectiveness results, CEACs and CEAFs for various scenario analyses
6 for proctitis are presented below.

SA2: No early switching of treatments in the event of non-remission

This scenario analysis assumes there is no early assessment of response to treatment. All people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome is remission or non-remission.

Table 76 shows an increase in costs for all sequences in this scenario analysis but sequences that start with topical aminosalicylate still dominate. As Figure 51 shows, PRC01 retains the highest probability of being cost effective and the highest expected net benefit over the range of threshold values from £0/QALY to £50,000/QALY.

Table 76: SA2 cost-effectiveness results for proctitis with no early switching of treatments in the event of non-remission

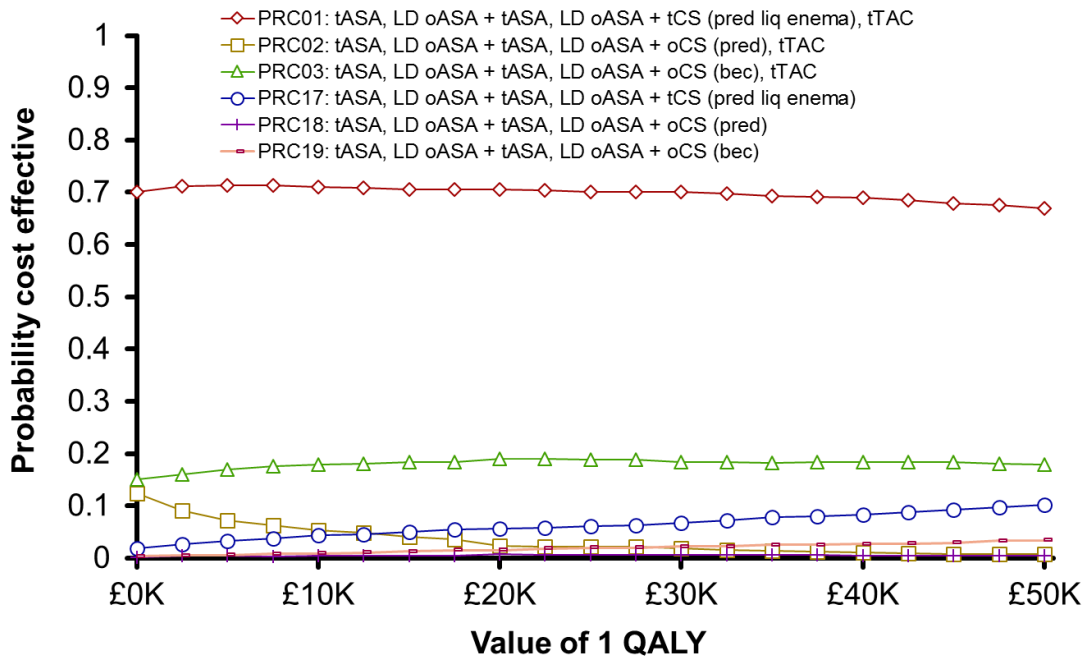
Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC01	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£460	0.5298				70.6%	£10,136
PRC03	tASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£471	0.5296	£11	-0.0002	dominated	19.0%	£10,120
PRC02	tASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£478	0.5288	£17	-0.0010	dominated	2.4%	£10,099
PRC04	tASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£502	0.5284	£42	-0.0014	dominated	0.0%	£10,067
PRC17	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£504	0.5300	£44	0.0002	£216,601	5.6%	£10,096
PRC19	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£529	0.5298	£25	-0.0002	dominated	1.5%	£10,068
PRC18	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£548	0.5292	£44	-0.0009	dominated	0.7%	£10,035
PRC20	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£598	0.5289	£94	-0.0011	dominated	0.0%	£9,980
PRC05	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£710	0.5069	£206	-0.0231	dominated	0.0%	£9,428
PRC09	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£747	0.5158	£243	-0.0143	dominated	0.2%	£9,568
PRC07	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£748	0.5061	£244	-0.0239	dominated	0.0%	£9,373
PRC13	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£754	0.5152	£250	-0.0148	dominated	0.0%	£9,551
PRC06	LD oASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£774	0.5032	£270	-0.0269	dominated	0.0%	£9,289
PRC11	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£809	0.5146	£305	-0.0155	dominated	0.0%	£9,482

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC15	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£819	0.5139	£314	-0.0162	dominated	0.0%	£9,458
PRC10	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£854	0.5095	£349	-0.0205	dominated	0.0%	£9,336
PRC14	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£863	0.5088	£359	-0.0212	dominated	0.0%	£9,312
PRC08	LD oASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£864	0.5017	£360	-0.0284	dominated	0.0%	£9,169
PRC21	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£873	0.5076	£368	-0.0224	dominated	0.0%	£9,280
PRC23	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£964	0.5071	£460	-0.0229	dominated	0.0%	£9,178
PRC12	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£1,006	0.5069	£502	-0.0231	dominated	0.0%	£9,133
PRC25	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,019	0.5170	£515	-0.0130	dominated	0.0%	£9,321
PRC16	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£1,020	0.5061	£515	-0.0239	dominated	0.0%	£9,103
PRC29	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,034	0.5165	£530	-0.0135	dominated	0.0%	£9,296
PRC22	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,043	0.5044	£539	-0.0256	dominated	0.0%	£9,045
PRC27	LD oASA + tASA, LD oASA + oCS (beclo)	£1,167	0.5162	£662	-0.0138	dominated	0.0%	£9,158
PRC31	LD oASA + tASA, LD oASA + oCS (beclo)	£1,189	0.5156	£685	-0.0145	dominated	0.0%	£9,122
PRC24	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,233	0.5034	£729	-0.0267	dominated	0.0%	£8,834
PRC26	LD oASA + tASA, LD oASA + oCS (pred)	£1,306	0.5115	£802	-0.0185	dominated	0.0%	£8,925
PRC30	LD oASA + tASA, LD oASA + oCS (pred)	£1,328	0.5109	£824	-0.0191	dominated	0.0%	£8,889
PRC28	LD oASA + tASA, LD oASA + oCS (bude)	£1,628	0.5098	£1,124	-0.0203	dominated	0.0%	£8,567
PRC32	LD oASA + tASA, LD oASA + oCS (bude)	£1,660	0.5091	£1,156	-0.0210	dominated	0.0%	£8,521

PRC = proctitis; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; tTAC = topical tacrolimus; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

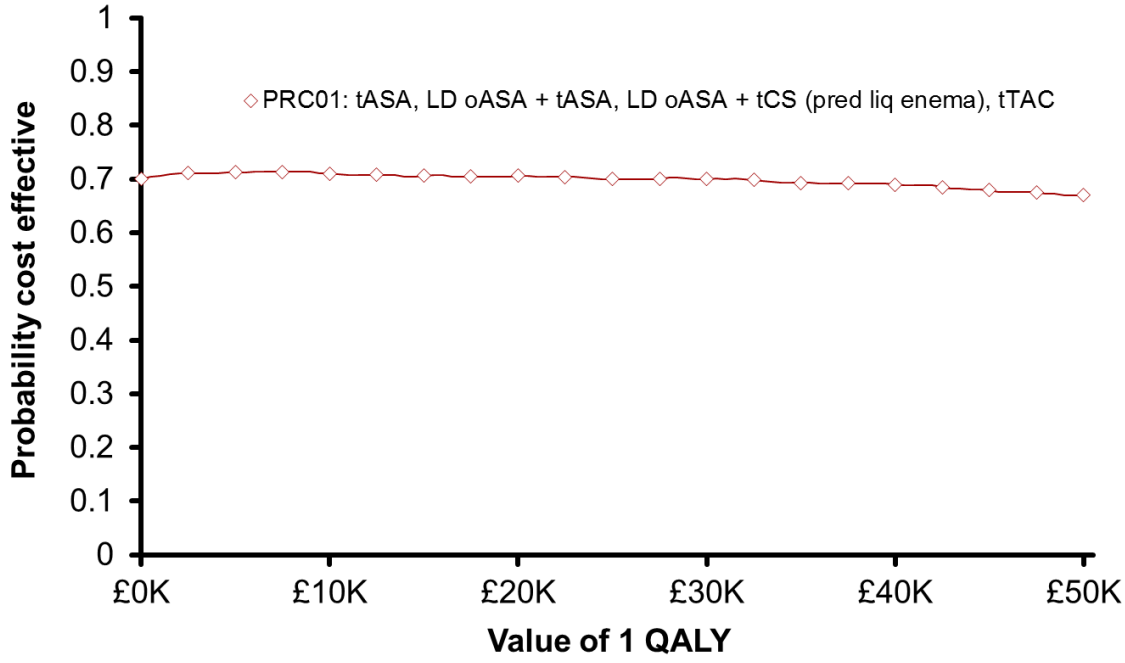
(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 50: SA2 cost-effectveness acceptability curve for proctitis with no early switching of treatments in the event of non-remission



1

Figure 51: SA2 cost-effectveness acceptability frontier for proctitis with no early switching of treatments in the event of non-remission



2

SA3: Duration of maintenance on biological therapies

This scenario analysis assumes that people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model.

There is an increase in costs for all sequwences but sequences that start with a topical aminosalicylate still dominate and PRC01 retains the highest expected net benefit over the range of threshold values from £0/QALY to £50,000/QALY.

Table 77: SA3 cost-effectiveness results for proctitis assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC01	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£448	0.5319				75.1%	£10,190
PRC03	tASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£460	0.5318	£12	-0.0002	dominated	16.7%	£10,175
PRC02	tASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£465	0.5313	£16	-0.0006	dominated	2.9%	£10,162
PRC04	tASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£485	0.5311	£36	-0.0008	dominated	0.0%	£10,138
PRC17	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£488	0.5320	£40	0.0001	£357,039	3.7%	£10,153
PRC19	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£519	0.5319	£31	-0.0001	dominated	1.2%	£10,120
PRC18	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£533	0.5315	£46	-0.0005	dominated	0.4%	£10,097
PRC20	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£581	0.5314	£93	-0.0006	dominated	0.0%	£10,047
PRC05	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£669	0.5180	£181	-0.0140	dominated	0.0%	£9,692
PRC09	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£701	0.5231	£213	-0.0089	dominated	0.0%	£9,762
PRC13	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£704	0.5230	£216	-0.0090	dominated	0.0%	£9,756
PRC07	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£714	0.5175	£226	-0.0146	dominated	0.0%	£9,636
PRC06	LD oASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£733	0.5155	£245	-0.0166	dominated	0.0%	£9,577

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC11	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£777	0.5223	£289	-0.0098	dominated	0.0%	£9,668
PRC15	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£782	0.5220	£294	-0.0100	dominated	0.0%	£9,659
PRC10	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£811	0.5189	£324	-0.0132	dominated	0.0%	£9,566
PRC08	LD oASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£814	0.5147	£327	-0.0174	dominated	0.0%	£9,479
PRC14	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£816	0.5186	£328	-0.0134	dominated	0.0%	£9,557
PRC21	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£828	0.5185	£341	-0.0136	dominated	0.0%	£9,541
PRC23	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£948	0.5181	£460	-0.0139	dominated	0.0%	£9,415
PRC12	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£952	0.5175	£464	-0.0145	dominated	0.0%	£9,398
PRC16	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£958	0.5173	£470	-0.0148	dominated	0.0%	£9,387
PRC25	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£978	0.5239	£491	-0.0082	dominated	0.0%	£9,499
PRC29	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£985	0.5237	£498	-0.0083	dominated	0.0%	£9,489
PRC22	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,007	0.5163	£519	-0.0158	dominated	0.0%	£9,319
PRC27	LD oASA + tASA, LD oASA + oCS (beclo)	£1,181	0.5233	£693	-0.0087	dominated	0.0%	£9,286
PRC31	LD oASA + tASA, LD oASA + oCS (beclo)	£1,192	0.5231	£704	-0.0089	dominated	0.0%	£9,271
PRC24	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,207	0.5158	£719	-0.0163	dominated	0.0%	£9,109
PRC26	LD oASA + tASA, LD oASA + oCS (pred)	£1,289	0.5202	£801	-0.0119	dominated	0.0%	£9,114
PRC30	LD oASA + tASA, LD oASA + oCS (pred)	£1,300	0.5200	£812	-0.0121	dominated	0.0%	£9,099
PRC28	LD oASA + tASA, LD oASA + oCS (bude)	£1,638	0.5193	£1,151	-0.0127	dominated	0.0%	£8,748
PRC32	LD oASA + tASA, LD oASA + oCS (bude)	£1,655	0.5191	£1,167	-0.0129	dominated	0.0%	£8,728

PRC = proctitis; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; tTAC = topical tacrolimus; pred = prednisolone; beclo =

Treatment sequence	Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
	Costs	QALYs	Costs	QALYs	ICER		
beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life yeare							

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 52: SA3 cost-effectiveness acceptability curve for proctitis assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model

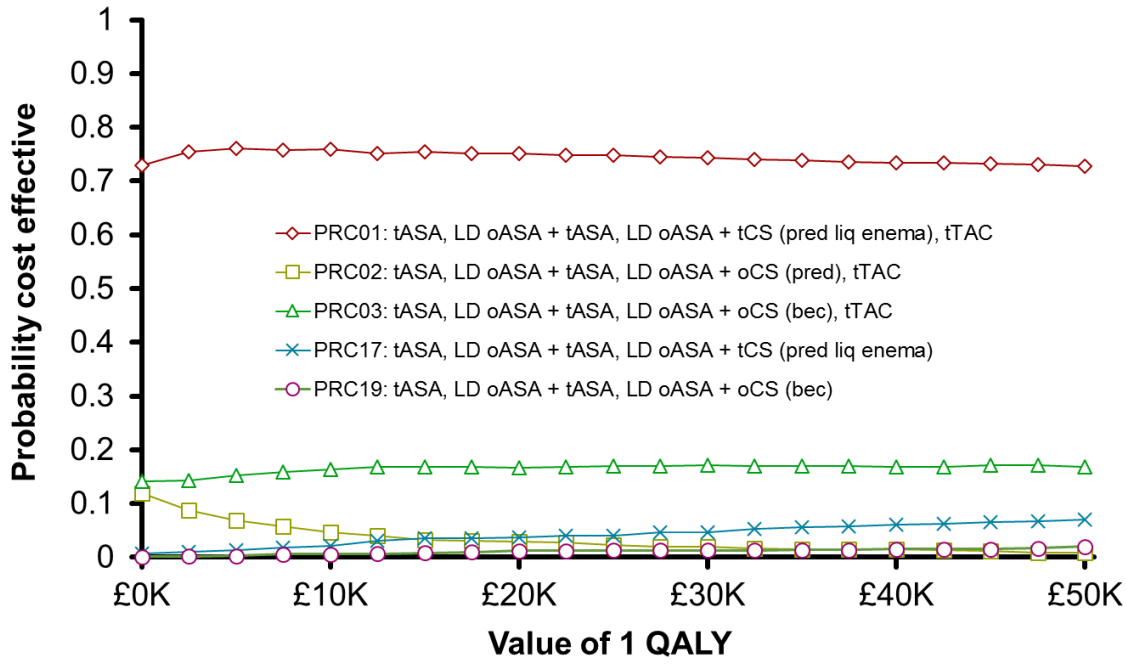
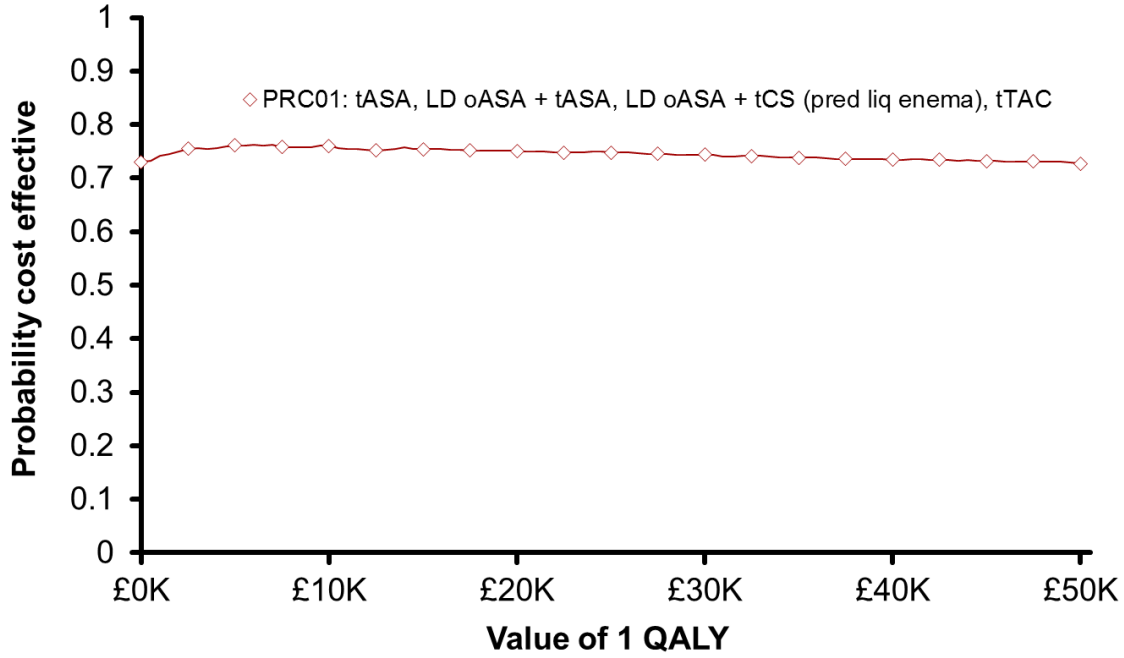


Figure 53: SA3 cost-effectiveness acceptability frontier for proctitis assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model



SA4: Vary drug price for topical prednisolone and topical tacrolimus

This scenario analysis varied the price of topical prednisolone from £7.50 to £77.06 to reflect the price of the suppository formulation instead of the liquid enema and also varied the price of topical tacrolimus from £16.55 to £47.56 to reflect the estimated cost of preparing a suppository on a case by case basis instead of using the ointment preparation. In this scenario, PRC03 is the least costly strategy and has the highest expected net benefit up to a threshold value of £24,000/QALY, at which point the optimal strategy becomes PRC01.

Table 78: SA4 cost-effectiveness results for proctitis varying the cost of topical prednisolone and topical tacrolimus

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC03	tASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£465	0.5318				40.1%	£10,170
PRC01	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£469	0.5319	£3	0.0001	£23,787	46.0%	£10,169
PRC02	tASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£470	0.5313	£1	-0.0006	dominated	2.7%	£10,156
PRC04	tASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£493	0.5311	£24	-0.0008	dominated	0.0%	£10,129

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC17	tASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£503	0.5320	£34	0.0001	£314,533	7.2%	£10,137
PRC19	tASA, LD oASA + tASA, LD oASA + oCS (beclo)	£517	0.5319	£14	-0.0001	dominated	3.8%	£10,121
PRC18	tASA, LD oASA + tASA, LD oASA + oCS (pred)	£529	0.5315	£26	-0.0005	dominated	0.2%	£10,101
PRC20	tASA, LD oASA + tASA, LD oASA + oCS (bude)	£577	0.5314	£74	-0.0006	dominated	0.0%	£10,050
PRC07	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£735	0.5174	£232	-0.0146	dominated	0.0%	£9,612
PRC05	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£752	0.5180	£248	-0.0140	dominated	0.0%	£9,608
PRC06	LD oASA, LD oASA + tASA, LD oASA + oCS (pred), tTAC	£759	0.5154	£256	-0.0166	dominated	0.0%	£9,549
PRC11	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£803	0.5222	£299	-0.0098	dominated	0.0%	£9,641
PRC15	LD oASA + tASA, LD oASA + oCS (beclo), tTAC	£808	0.5220	£304	-0.0100	dominated	0.0%	£9,632
PRC09	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£832	0.5231	£329	-0.0089	dominated	0.0%	£9,629
PRC13	LD oASA + tASA, LD oASA + tCS (pred liq enema), tTAC	£838	0.5229	£334	-0.0091	dominated	0.0%	£9,621
PRC10	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£843	0.5188	£340	-0.0132	dominated	0.0%	£9,533
PRC14	LD oASA + tASA, LD oASA + oCS (pred), tTAC	£848	0.5186	£345	-0.0134	dominated	0.0%	£9,523
PRC08	LD oASA, LD oASA + tASA, LD oASA + oCS (bude), tTAC	£854	0.5146	£351	-0.0175	dominated	0.0%	£9,437
PRC21	LD oASA, LD oASA + tASA, LD oASA + tCS (pred liq enema)	£892	0.5184	£389	-0.0136	dominated	0.0%	£9,476
PRC23	LD oASA, LD oASA + tASA, LD oASA + oCS (beclo)	£945	0.5180	£441	-0.0140	dominated	0.0%	£9,416
PRC12	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£1,003	0.5174	£500	-0.0146	dominated	0.0%	£9,344
PRC22	LD oASA, LD oASA + tASA, LD oASA + oCS (pred)	£1,003	0.5162	£500	-0.0158	dominated	0.0%	£9,320
PRC16	LD oASA + tASA, LD oASA + oCS (bude), tTAC	£1,010	0.5171	£507	-0.0149	dominated	0.0%	£9,332

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
PRC25	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,065	0.5238	£562	-0.0082	dominated	0.0%	£9,412
PRC29	LD oASA + tASA, LD oASA + tCS (pred liq enema)	£1,073	0.5237	£570	-0.0083	dominated	0.0%	£9,400
PRC27	LD oASA + tASA, LD oASA + oCS (beclo)	£1,148	0.5232	£644	-0.0088	dominated	0.0%	£9,317
PRC31	LD oASA + tASA, LD oASA + oCS (beclo)	£1,159	0.5230	£655	-0.0090	dominated	0.0%	£9,302
PRC24	LD oASA, LD oASA + tASA, LD oASA + oCS (bude)	£1,209	0.5157	£706	-0.0163	dominated	0.0%	£9,104
PRC26	LD oASA + tASA, LD oASA + oCS (pred)	£1,250	0.5201	£747	-0.0119	dominated	0.0%	£9,151
PRC30	LD oASA + tASA, LD oASA + oCS (pred)	£1,261	0.5199	£758	-0.0122	dominated	0.0%	£9,136
PRC28	LD oASA + tASA, LD oASA + oCS (bude)	£1,596	0.5192	£1,093	-0.0128	dominated	0.0%	£8,788
PRC32	LD oASA + tASA, LD oASA + oCS (bude)	£1,612	0.5190	£1,109	-0.0130	dominated	0.0%	£8,768

PRC = proctitis; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; tCS = topical corticosteroid; tTAC = topical tacrolimus; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 54: SA4 cost-effectiveness acceptability curve for proctitis varying the cost of topical prednisolone and topical tacrolimus

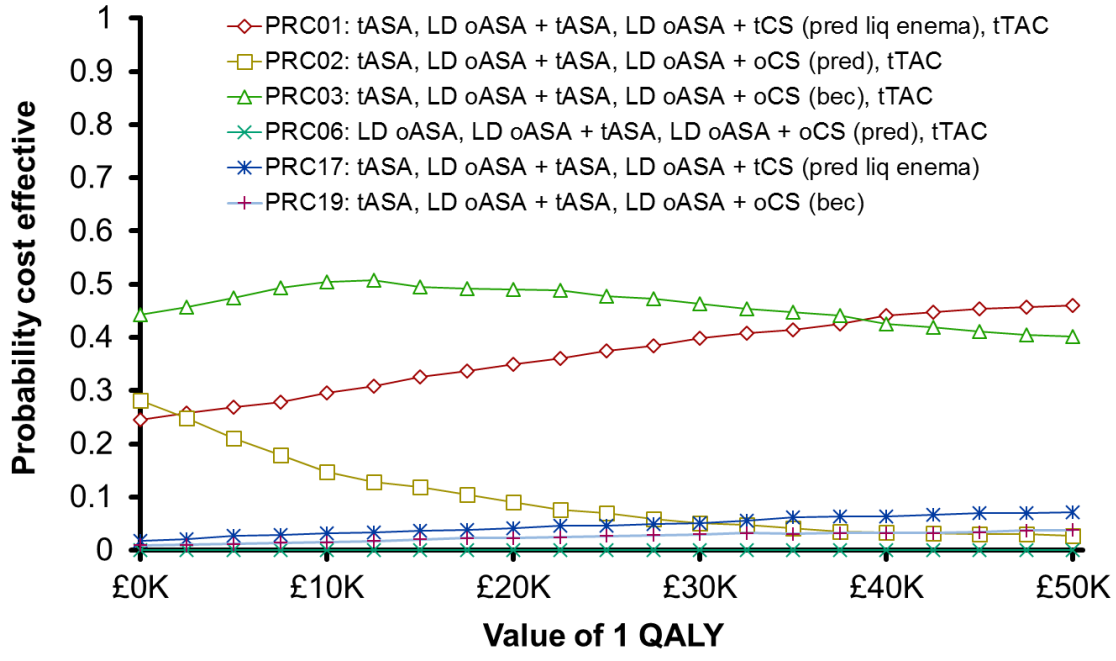
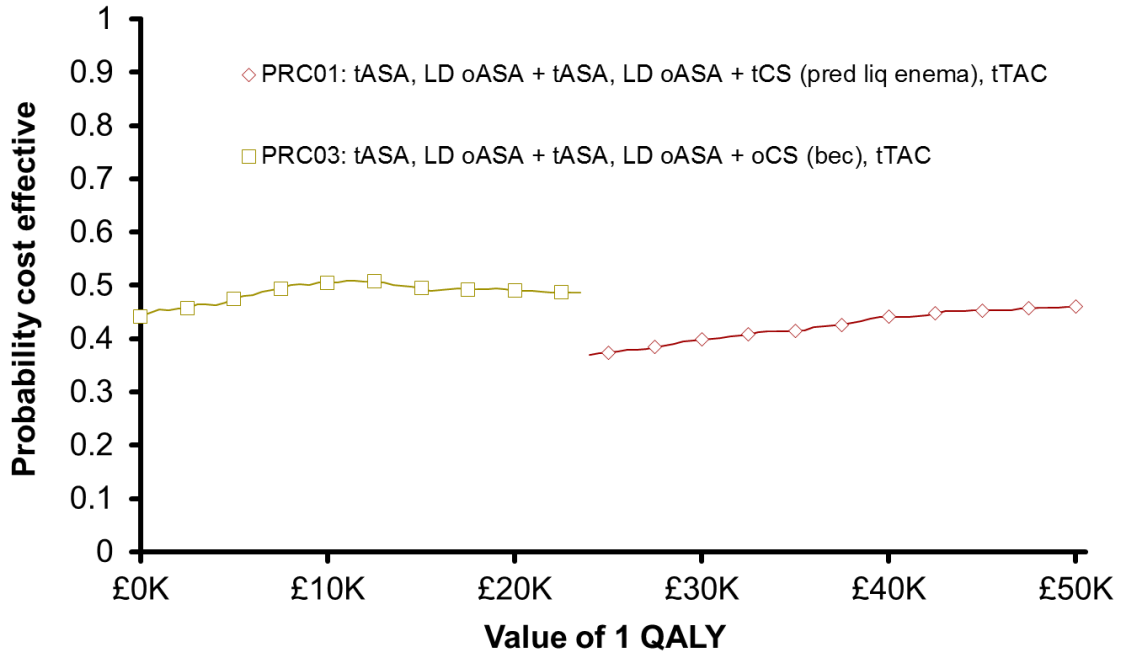


Figure 55: SA4 cost-effectiveness acceptability frontier for proctitis varying the cost of topical prednisolone and topical tacrolimus



L.3.3 Extensive disease

L.3.3.1 Remission by line of treatment

Table 79 shows the proportion of people whose disease entered clinical remission in each line of treatment for each sequence in the base-case analysis for extensive disease. Sequences that begin with the combination of a high-dose oral aminosalicylate and topical aminosalicylate (EXT04 – EXT06) have a higher proportion of people entering remission in first line (68.3%) but also a higher proportion of people requiring rescue therapy (9.7% - 23.0%). This is beause it was only possible model up to two lines of treatment in the sequences that begin with the combination of a high-dose oral aminosalicylate and topical aminosalicylate. The average number of weeks spent with active disease is lower for the sequences that begin with combination treatment (4.8 – 5.6 weeks).

Table 79 also shows the costs of each treatment sequence broken down into the following categories: cost of drugs for induction of remission, cost of rescue therapy, cost of other healthcare resource use (consultant, nurse, GP, outpatient appointments, A&E attendances and blood tests) and cost of maintenance treatment. The widest variation in absolute costs is seen with rescue therapy (range £164- £726), suggesting that the proportion of patients requiring rescue therapy accounts for the biggest differences in costs when comparing treatment sequences.

Table 79: Proportion of people whose disease enters remission by line of treatment, average time spent in active disease vs. remission and breakdown of costs for each treatment sequence in base-case analysis for extensive disease

Treatment sequence		Proportion entering remission				Weeks active	Weeks remission	Costs				
		1st line	2nd line	3rd line	Rescue			Drug	Rescue	Other healthcare	Maintenance	Total
EXT01	HD oASA, HD oASA + tASA, LD oASA + oCS (bude)	48.5%	34.6%	4.6%	12.3%	6.9	23.1	£296	£389	£303	£120	£1,108
EXT02	HD oASA, HD oASA + tASA, LD oASA + oCS (beclo)	48.5%	34.6%	11.7%	5.2%	6.4	23.6	£288	£164	£292	£122	£866
EXT03	HD oASA, HD oASA + tASA, LD oASA + oCS (pred)	48.5%	34.6%	10.6%	6.3%	6.8	23.2	£286	£199	£295	£119	£899
EXT04	HD oASA + tASA, LD oASA + oCS (bude)	68.3%	8.6%	0.0%	23.0%	5.6	24.4	£359	£726	£262	£130	£1,477
EXT05	HD oASA + tASA, LD oASA + oCS (beclo)	68.3%	21.9%	0.0%	9.7%	4.8	25.2	£343	£307	£242	£134	£1,026
EXT06	HD oASA + tASA, LD oASA + oCS (pred)	68.3%	19.9%	0.0%	11.8%	5.4	24.6	£340	£372	£247	£128	£1,087

EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide

L.3.3.12 Cost-effectiveness results

Table 80 summarises the base case cost-effectiveness results in extensive disease with sequences ordered from least costly to most costly. Treatment sequences EXT02 and EXT03, which begin with a high-dose oral aminosalicylate given alone and differ only in terms of the oral corticosteroid assumed in third line, produce similar costs and QALYs. In comparison to EXT02 the sequence EXT05, which begins with the combination of a high-dose oral aminosalicylate and topical aminosalicylate, produces an ICER of £34,091/QALY. All other treatment sequences are dominated.

Table 80: Base-case cost-effectiveness results for extensive disease

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
EXT02	HD oASA, HD oASA + tASA, LD oASA + oCS (beclo)	£888	0.5198				42.7%	£9,508
EXT03	HD oASA, HD oASA + tASA, LD oASA + oCS (pred)	£921	0.5186	£33	-0.0012	dominated	26.5%	£9,451
EXT05	HD oASA + tASA, LD oASA + oCS (beclo)	£1,060	0.5248	£172	0.0051	£34,091	22.9%	£9,436
EXT06	HD oASA + tASA, LD oASA + oCS (pred)	£1,118	0.5226	£58	-0.0022	dominated	7.7%	£9,335
EXT01	HD oASA, HD oASA + tASA, LD oASA + oCS (bude)	£1,125	0.5180	£65	-0.0068	dominated	0.2%	£9,236
EXT04	HD oASA + tASA, LD oASA + oCS (bude)	£1,495	0.5216	£435	-0.0032	dominated	0.0%	£8,937

EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 56: Cost-effectiveness acceptability curve for extensive disease case-case analysis

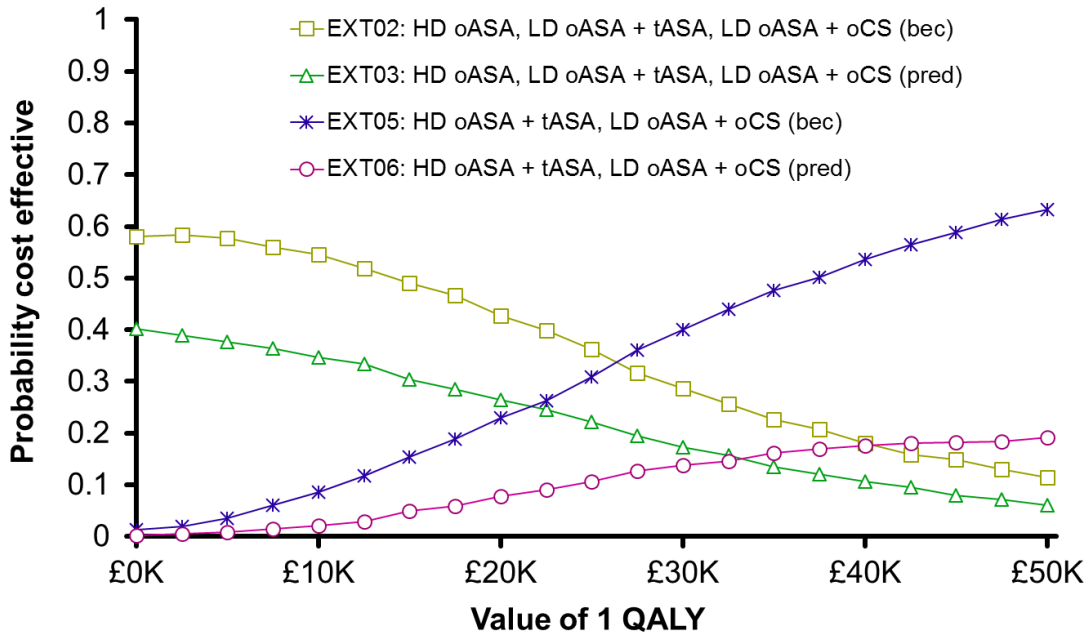


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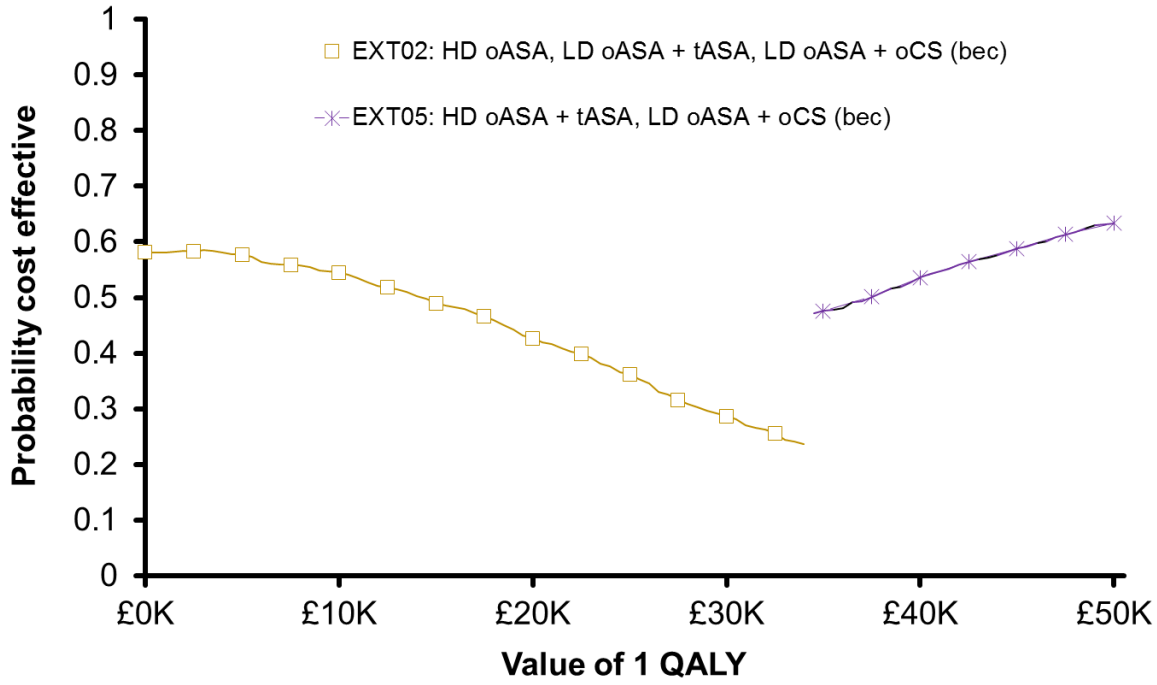
Figure 57: Cost-effectiveness acceptability frontier for extensive disease base-case analysis



L.3.3.13 Scenario analyses

The incremental cost-effectiveness results, CEACs and CEAFs for various scenario analyses for extensive disease are presented below.

SA2: No early switching of treatments in the event of non-remission

This scenario analysis assumes there is no early assessment of response to treatment. All people, except those withdrawing due to adverse events, are assumed to complete a full course treatment irrespective of whether the outcome is remission or non-remission. The ICER for the comparison of EXT05 with EXT02 has fallen from a value of £34,091/QALY in the base-case analysis to £16,671/QALY.

Table 81: SA2 cost-effectiveness results for extensive disease with no early switching of treatments in the event of non-remission

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
EXT02	HD oASA, HD oASA + tASA, LD oASA + oCS (beclo)	£964	0.5106				20.8%	£9,248
EXT03	HD oASA, HD oASA + tASA, LD oASA + oCS (pred)	£1,014	0.5088	£50	-0.0018	dominated	11.3%	£9,162
EXT05	HD oASA + tASA, LD oASA + oCS (beclo)	£1,124	0.5202	£160	0.0096	£16,671	52.9%	£9,280
EXT06	HD oASA + tASA, LD oASA + oCS (pred)	£1,209	0.5170	£85	-0.0032	dominated	15.0%	£9,131
EXT01	HD oASA, HD oASA + tASA, LD oASA + oCS (bude)	£1,231	0.5075	£107	-0.0127	dominated	0.0%	£8,919
EXT04	HD oASA + tASA, LD oASA + oCS (bude)	£1,589	0.5147	£466	-0.0054	dominated	0.0%	£8,705

EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 58: SA2 cost-effectiveness acceptability curve for extensive disease with no early switching of treatments in the event of non-remission

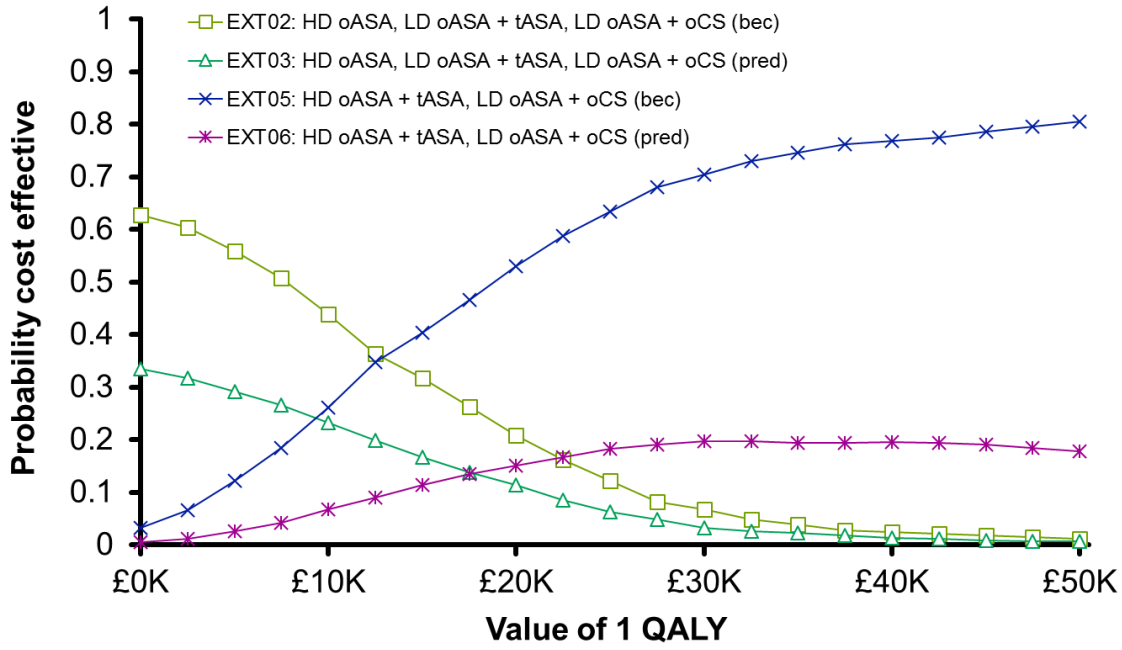
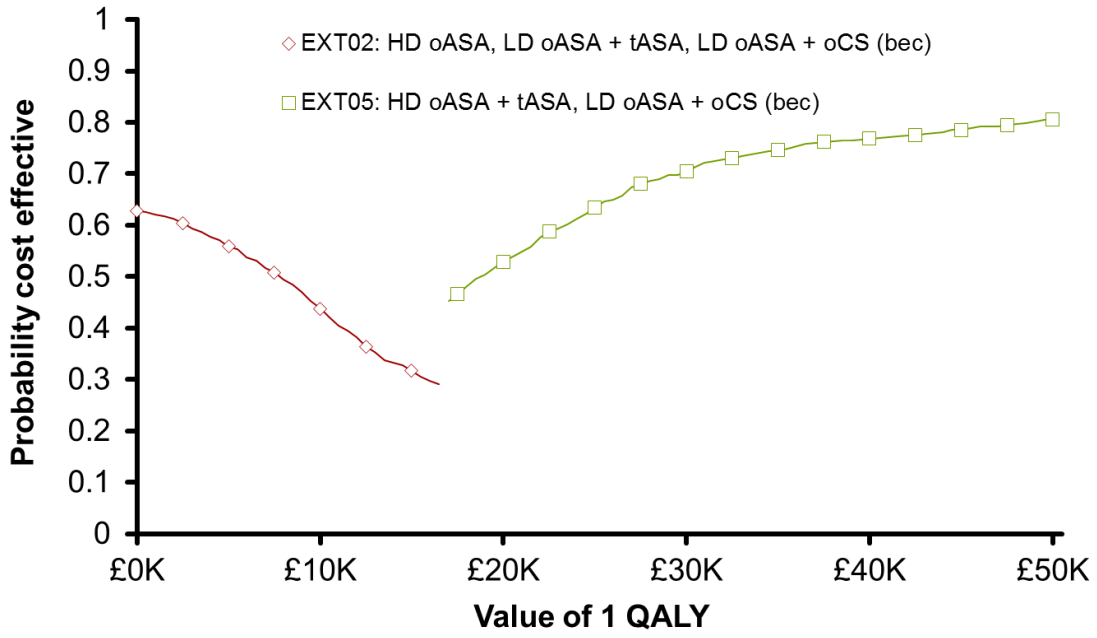


Figure 59: SA2 cost-effectiveness acceptability frontier for extensive disease with no early switching of treatments in the event of non-remission



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SA3: Duration of maintenance on biological therapies

This scenario analysis assumes that people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model. Compared to the base case, there is a small increase in costs for all sequences in this scenario analysis and the ICER for the comparison of EXT05 with EXT02 has risen to £38,445/QALY.

Table 82: SA3 deterministic cost-effectiveness results for extensive assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model

Treatment sequence		Total		Incremental			Prob CE at £20K/ QALY	NMB at £20K/ QALY
		Costs	QALYs	Costs	QALYs	ICER		
EXT02	HD oASA, HD oASA + tASA, LD oASA + oCS (beclo)	£898	0.5198				46.0%	£9,499
EXT03	HD oASA, HD oASA + tASA, LD oASA + oCS (pred)	£934	0.5186	£36	-0.0012	dominated	30.2%	£9,439
EXT05	HD oASA + tASA, LD oASA + oCS (beclo)	£1,092	0.5249	£194	0.0051	£38,445	19.4%	£9,406
EXT06	HD oASA + tASA, LD oASA + oCS (pred)	£1,144	0.5181	£52	-0.0068	dominated	0.1%	£9,218
EXT01	HD oASA, HD oASA + tASA, LD oASA + oCS (bude)	£1,156	0.5227	£64	-0.0022	dominated	4.3%	£9,298
EXT04	HD oASA + tASA, LD oASA + oCS (bude)	£1,559	0.5217	£467	-0.0032	dominated	0.0%	£8,875

EXT = extensive disease; LD = low-dose; HD = high-dose; oASA = oral aminosalicylate; tASA = topical aminosalicylate; oCS = oral corticosteroid; pred = prednisolone; beclo = beclometasone; bude = budesonide; CE = cost effective; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality-adjusted life year

(a) Treatment strategies that are dominated are more costly and produce fewer QALYs than one or more of the alternative treatment strategies in the decision space

Figure 60: SA3 cost-effectiveness acceptability curve for extensive disease assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model

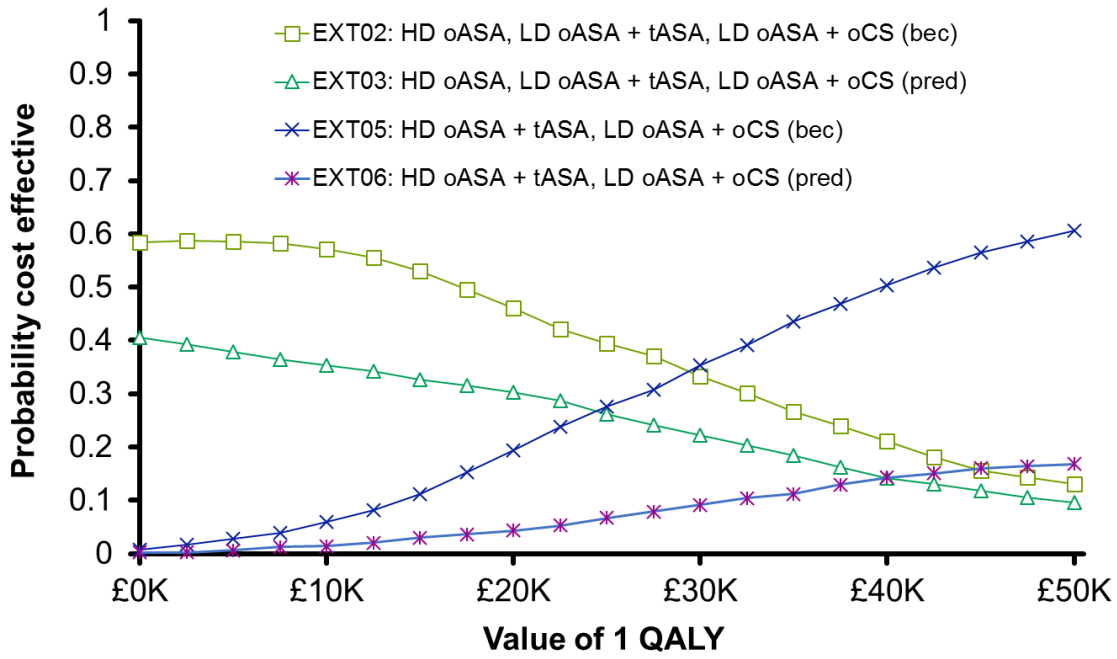
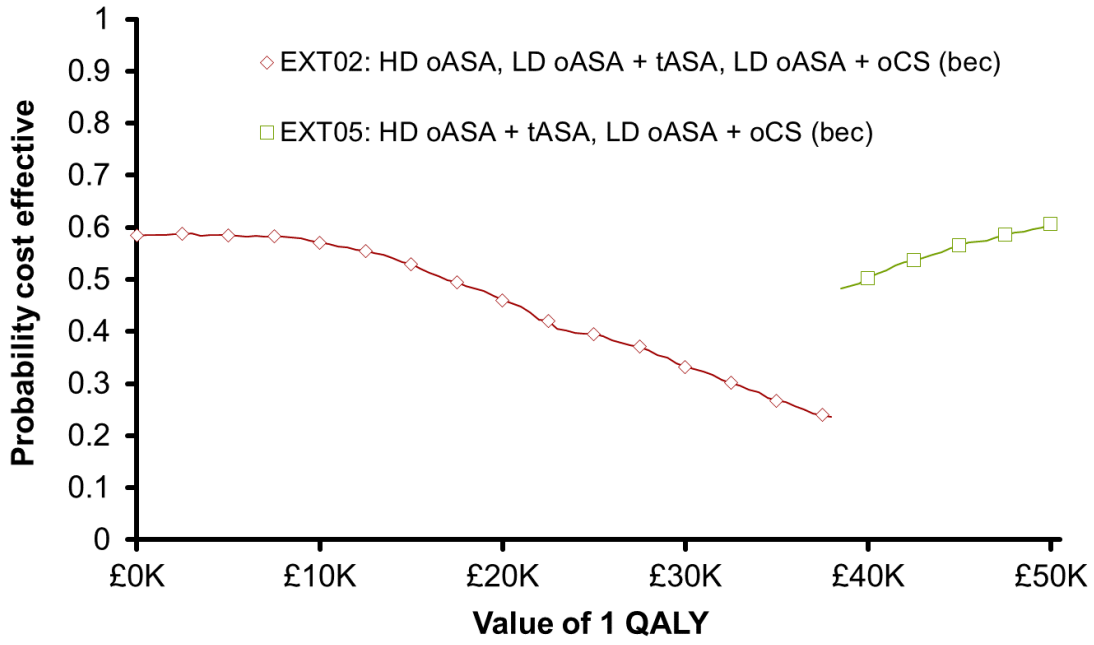


Figure 61: SA3 cost-effectiveness acceptability frontier for extensive disease assuming people whose disease is responding to biological drugs as part of rescue therapy continue to receive treatment for the remaining time horizon of the model



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L.4 Discussion

L.4.1 Main findings

This cost-effectiveness analysis was undertaken to compare sequences of treatments for the induction of remission of mild-to-moderate ulcerative colitis by extent of disease. The results suggest:

- In proctosigmoiditis and left-sided disease, treatment sequences that begin with a topical aminosalicylate in first line followed by the addition of an oral aminosalicylate in second line and then a topical or oral corticosteroid in third line result in more QALYs and lower costs and dominate all other treatment strategies. There was not a strong basis for differentiating between treatment strategies in terms of the choice of corticosteroid in third line. The committee discussed whether the dose of the oral aminosalicylate in second line should be low or high. Based on the available RCT evidence in proctosigmoiditis and left-sided disease, it was only possible to model low-dose oral aminosalicylates in combination with a topical aminosalicylate as part of treatment sequences. However, the committee noted the superior efficacy of high-dose oral aminosalicylates in comparison to low-dose oral aminosalicylates and decided to infer that this was likely to hold when used in combination with a topical aminosalicylate.
- In proctitis, treatment sequences that begin with a topical aminosalicylate in first line followed by the addition of an oral aminosalicylate in second line, a topical or oral corticosteroid in third line and topical tacrolimus in fourth line result in more QALYs and lower costs and dominate all other treatment strategies. The committee noted that the evidence to inform the remission rate for topical tacrolimus was based on 1 RCT of 20 participants and that the preparation used in the trial did not reflect UK clinical practice or costs. Given this uncertainty, all treatment sequences in proctitis were modelled both with and without topical tacrolimus as a fourth line option. When omitting topical tacrolimus, treatment sequences that begin with a topical aminosalicylate in first line followed by the addition of an oral aminosalicylate in second line and a topical or oral corticosteroid in third line remain cost effective. Again, there was not a strong basis for differentiating between treatment strategies in terms of the choice of corticosteroid (oral or topical) in third line.
- In extensive disease, treatment sequences that begin with the combination of a high-dose oral aminosalicylate and a topical aminosalicylate generate more QALYs but also higher costs than sequences that begin with a high-dose oral aminosalicylate alone. This is because, based on the limited amount of RCT evidence in extensive disease, it was not possible to specify a third-line treatment option for sequences that begin with the combination treatment, resulting in higher proportions of patients requiring rescue therapy. In the base case, the ICER for EXT05 (high-dose oral aminosalicylate + topical aminosalicylate in first line followed by oral belcometasone in second line) versus EXT02 (high-dose oral aminosalicylate in first line followed by the addition of a topical aminosalicylate in second line and then oral beclometasone in third line) was £34,091/QALY. The ICER fell to £16,671/QALY in a scenario analysis in which it was assumed there was no early switching of treatments in the event of non-response.

L.4.2 Strengths and limitations

The committee felt that sequencing of treatments for the induction of remission of mild-to-moderate ulcerative colitis was an area of both clinical and economic uncertainty where modelling would be informative. The main strength of this analysis is that it incorporates new RCT evidence that has emerged since the 2013 guideline was produced, expands the

number of treatment sequences under comparison, updates the assumptions about rescue therapy to reflect current practice and produces separate cost-effectiveness results for each extent of disease. The model makes use of all available data by drawing on evidence synthesised using network meta-analysis to estimate the relative effects of all treatments of interest in terms of both withdrawal due to adverse events and probability of achieving remission. However, there are a number of important assumptions and limitations to consider:

- RCT evidence was categorised by extent of disease and duration of follow-up, which resulted in sparse evidence networks for proctitis and extensive disease. Sparseness of data and small sample sizes resulted in high levels of uncertainty in the estimates of relative effectiveness for a number of comparisons. This uncertainty was considered in probabilistic sensitivity analyses but given the structural assumptions of the cost-effectiveness model, this had relatively little impact on the overall conclusions. Due to the limited number of RCTs conducted specifically in proctitis, it was necessary to borrow estimates of relative effectiveness for several drugs from proctosigmoiditis and left-sided disease in order to model a number of treatment sequences. The results in proctitis should be interpreted with caution.
- In early committee discussions about the structure for the cost-effectiveness model, two important discrepancies between the design of clinical trials and current clinical practice emerged. The first was that the duration of follow-up in trials for some of the drugs did not match the committee's experience regarding duration of treatment in practice. This resulted in a mismatch between the timepoint at which remission was reported in some RCTs for some drugs and the assumption about duration (and therefore cost) of treatment in the cost-effectiveness model. Taking a conservative approach, if the trial duration was shorter than the duration of treatment in clinical practice, the model allowed for remission rates from an earlier time point to be applied at a later time point in the model but not the inverse. This meant that 2 drugs, topical hydrocortisone and topical budesonide, could not be modelled in the base case analysis but were included in sensitivity analyses for proctosigmoiditis and left-sided disease. The second discrepancy that emerged is that, in clinical practice, an assessment of response to treatment would generally take place approximately halfway through a full course of treatment so that people whose disease was not responding to treatment could be switched to another treatment. The base case analyses allowed for early treatment switching to take place but could lead to underestimation of treatment costs in relation to treatment benefits reported in RCTs. To address this issue, sensitivity analyses were run for each extent of disease in which no early treatment switching was permitted.
- In line with the clinical evidence review, induction of remission was the primary outcome of interest in the economic model. There was no evidence to suggest different treatments would have any impact on mortality rates. The choice of time horizon for the model was therefore a pragmatic balance between being long enough to reflect the time it would take to achieve remission but short enough to assume that once remission was achieved, everyone in the model would remain in remission for the duration of the analysis. Disease relapse was not modelled. The differences in QALYs between treatment sequences is therefore driven by the proportion of people and amount of time spent in remission versus active disease over the 30-week time horizon. This resulted in very small differences in QALYs across sequences.
- In the model, if induction of remission was not achieved following treatment with one of the drugs under comparison, a standard assumption about rescue therapy was applied to all arms in the decision tree. The costs associated with rescue therapy for treating severe disease are much higher than the costs associated with drugs for the induction of remission of mild-to-moderate disease. As the model results demonstrate, costs were most sensitive to the proportion of people requiring rescue therapy. To maintain structural coherence, the model did not consider potential long-term differences in QALYs and costs beyond achieving remission. For example, it did not take into account the long-term

impact of surgery on health-state utilities, costs associated with post-surgical care, costs of long-term maintenance with biological therapies or costs associated with treating subsequent relapses. All of these longer-term consequences are expected to increase downstream costs and further amplify the importance of inducing remission as early as possible in the treatment sequence in order to avoid the need for rescue therapy.

L.4.3 Comparison with 2013 guideline economic model

No RCTs were identified that directly compare sequences of treatment for the induction of remission of mild-to-moderate ulcerative colitis. In order to evaluate the cost effectiveness of treatment sequences in both the 2013 model and the current model, it was necessary to make a number of strong assumptions:

- The probability of a person's disease entering remission is independent of the line of treatment in which a drug is used.
- Once a person's disease enters remission, it is assumed to remain in remission for the duration of the model.

Beyond these assumptions, there are a number of differences between the 2013 model and the current model that limit the comparability of results:

- The categorisation of extent of disease differs between the 2 analyses. The 2013 model considered adults with left-sided or extensive ulcerative colitis and all 10 treatment strategies began with an oral aminosalicylate either alone or in combination in first line. In the current analysis, extensive disease is considered as a separate subgroup and left-sided disease is grouped with proctosigmoiditis. In the latter subgroup, due to the location of disease distal to the splenic flexure, topical aminosalicylates are a relevant first-line treatment option. The current analysis compared 32 treatment sequences in proctitis, 75 in proctosigmoiditis and left-sided disease and 6 in extensive disease.
- The 2013 model included the following comparators: low-dose oral aminosalicylates, high-dose oral aminosalicylates, topical aminosalicylates, oral beclometasone and prednisolone. For the current analysis, the following additional treatments were considered: oral budesonide, topical budesonide, topical hydrocortisone, topical prednisolone and topical tacrolimus.
- In the 2013 model, it was assumed that people who withdrew from treatment and people who did not respond to a given treatment went on to receive the same treatment in the following line of each sequence. The current model allowed for the next treatment in the sequence to differ following withdrawal due to adverse events and non-response to treatment.
- In both the 2013 model and the current model, there was insufficient data in RCTs to model remission conditional on response to treatment. In the 2013 model, it was assumed people would remain on treatment for the full duration regardless of whether the outcome was remission or non-remission. The current model permitted early switching to the next line of treatment for people whose disease did not enter remission but a sensitivity analysis was conducted adopting the approach taken in the 2013 model.
- In the 2013 model, the probability of remission conditional on non-withdrawal was estimated in the network meta-analysis by removing the number of withdrawals from the denominator when entering remission data. This approach was not adopted in the current model as a minority of studies reported both outcomes.
- In the 2013 model, rescue therapy comprised inpatient treatment with intravenous drugs or surgery. In the current model, the use of biological therapies to induce remission were modelled as part of rescue therapy, informed by national audit data.

L.4.4 Conclusions

Overall, the analyses demonstrate that in proctitis, proctosigmoiditis and left-sided disease, treatment sequences that start with a topical aminosalicylate, followed by the addition of an oral aminosalicylate and then either a topical or oral corticosteroid are cost effective because they result in the highest proportion of people whose disease enters remission as early as possible and the lowest proportion of people requiring hospitalisation and rescue therapy. In extensive disease, there was more uncertainty with respect to the optimal treatment sequence but a scenario analysis in which all people, other than those withdrawing due to adverse events, were assumed to receive a full course of treatment suggests that using a high-dose oral aminosalicylate in combination with a topical aminosalicylate in first line followed by an oral corticosteroid (in combination with an oral aminosalicylate) as second-line treatment is likely to be cost effective.

L.5 WinBUGS code for baseline synthesis

Baseline model clinical remission (fixed-effect)

```
# Binomial likelihood, logit link
# Fixed-effect model
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 5: Evidence synthesis in the baseline
# natural history model. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                    # indexes studies
  k[i]        ~  dbin(p[i], N[i])           # binomial likelihood
  logit(p[i]) <- m                          # model for linear predictor
  dummy[i]    <- Yrs[i]                     # not used in this model
  }                                         # close study loop
m ~  dnorm(0, 0.0001)                       # vague prior for baseline
logit(prob)  <- m                           # posterior probability of response
```

Baseline model clinical remission (random effects)

```
# Binomial likelihood, logit link
# Random effect model
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 5: Evidemce synthesis in the baseline
# natural history model. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                    # indexes studies
  k[i]        ~  dbin(p[i], N[i])           # binomial likelihood
  logit(p[i]) <- mu[i]                      # model for linear predictor
  mu[i]       ~  dnorm(m, tau.m)            # trial-specific baseline with random effects
  dummy[i]    <- Yrs[i]                     # not used in this model
  }                                         # close study loop
sd.m          ~  dunif(0, 5)                # vague prior for SD (baseline)
tau.m         <- pow(sd.m, -2)              # between-trial precision (baseline)
m             ~  dnorm(0, .0001)            # vague prior for mean (baseline)
logit(prob)  <- m                           # posterior probability of response
mu.new        ~  dnorm(m, tau.m)            # pred. dist. for baseline (log-odds)
logit(pred)  <- mu.new                      # predictive probability of response
}
```

Baseline model withdrawal due to adverse events (fixed-effect)

```
# Binomial likelihood, cloglog link
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 5: Evidemce synthesis in the baseline
# natural history model. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                    # indexes studies
  k[i]          ~  dbin(p[i], N[i])         # binomial likelihood
  cloglog(p[i]) <- log(Yrs[i]) + m          # model for linear predictor
  }                                         # close study loop
m ~  dnorm(0, 0.0001)                       # vague prior for baseline
cloglog(prob) <- log(1) + m                 # posterior mean yearly response rate
}
```

Baseline model withdrawal due to adverse events (random effects)

```
# Binomial likelihood, cloglog link
# based on
# Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E.
# NICE DSU Technical Support Document 5: Evidence synthesis in the baseline
# natural history model. 2011.
# http://www.nicedsu.org.uk

model {
for(i in 1:NumStudies) {                     # indexes studies
  k[i]          ~  dbin(p[i], N[i])          # binomial likelihood
  cloglog(p[i]) <- log(Yrs[i]) + mu[i]       # model for linear predictor
  mu[i]         ~  dnorm(m, tau.m)           # trial-specific baseline with random effects
  }                                          # close study loop
sd.m          ~  dunif(0, 5)                 # vague prior for SD (baseline)
tau.m         <- pow(sd.m, -2)               # between-trial precision (baseline)
m             ~  dnorm(0, .0001)             # vague prior for mean (baseline)
cloglog(prob) <- log(1) + m                  # posterior mean yearly response rate
mu.new        ~  dnorm(m, tau.m)             # pred. dist. for baseline (log-HR)
cloglog(pred) <- log(1) + mu.new             # predictive mean yearly response rate
}
```

1 Appendix M: Excluded studies

2 Clinical studies

3 Excluded studies which were included in 2013 guideline

Short Title	Title	Reasons for exclusion
Andus (2008)	A novel high-dose 1g mesalamine suppository (Salofalk) is as efficacious as a 500-mg TID suppositories in mild to moderate active ulcerative proctitis: A multicenter, randomized trial	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Andus (2010)	Clinical trial: a novel high-dose 1 g mesalamine suppository (Salofalk) once daily is as efficacious as a 500-mg suppository thrice daily in active ulcerative proctitis	Comparison not included.
Ardizzone (1999)	Mesalazine foam (Salofalk (R) foam) in the treatment of active distal ulcerative colitis. A comparative trial vs Salofalk (R) enema	Article unavailable: journal out of print or could not be sourced.
BARON (1962)	Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone	Comparison not included.
Baumgart (2008)	Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis	Systematic or narrative review: used to identify relevant references.
Biancone (2007)	Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: A multicenter, randomized, double-blind study	No outcomes in protocol reported.
Cai (2001)	Olsalazine versus sulfasalazine in the treatment of ulcerative colitis: Randomized controlled Clinical trial	Not in English.
Campieri (1988)	5-Aminosalicylic Acid As Enemas Or Suppositories in Distal Ulcerative-Colitis	RCT that did not contain a relevant comparison, as both arms were categorised as a topical aminosalicylate.
Campieri (1991)	Sucralfate, 5-Aminosalicylic Acid and Placebo Enemas in the Treatment of Distal Ulcerative-Colitis	Article unavailable: journal out of print or could not be sourced.
Campieri (1993)	Better Quality of Therapy with 5-Asa Colonic Foam in Active Ulcerative-Colitis – A Multicenter Comparative Trial with 5-Asa Enema	Preparation not available in the UK.
Cortot (2008)	Mesalamine Foam Enema Versus Mesalamine Liquid Enema in Active Left-Sided Ulcerative Colitis	RCT that did not contain a relevant comparison, as both arms were categorised as a topical aminosalicylate.
Danielsson (1987)	A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis	Preparation not available in the UK.

Short Title	Title	Reasons for exclusion
Farup (1995)	Mesalazine Suppositories Versus Hydrocortisone Foam in Patients with Distal Ulcerative-Colitis - A Comparison of the Efficacy and Practicality of 2 Topical Treatment Regimens	Preparation not available in the UK.
Farup (2001)	Mesalazine 4 g daily given as prolonged-release granules twice daily and four times daily is at least as effective as prolonged-release tablets four times daily in patients with ulcerative colitis	Comparison not included. Info: Comparison of different oral preparations of mesalazine.
Ferry (1993)	Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial	RCT that did not contain a relevant comparison, as both arms were categorised as standard-dose oral aminosalicylates.
Forbes (2005)	Multicentre randomized-controlled clinical trial of Ipocol, a new enteric-coated form of mesalazine, in comparison with Asacol in the treatment of ulcerative colitis	Comparison not included.
Friedman (1986)	5-Aminosalicylic Acid Enemas in Refractory Distal Ulcerative-Colitis - A Randomized, Controlled Trial	Preparation not available in the UK.
Gibson (2006)	Comparison of the efficacy and safety of Eudragit-L-coated mesalazine tablets with ethylcellulose-coated mesalazine tablets in patients with mild to moderately active ulcerative colitis	RCT that did not contain a relevant comparison, as both arms were categorised as standard-dose oral aminosalicylates.
Green (1998)	Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis	>10% of study population had severe ulcerative colitis.
Hanauer (1996)	A multi-center, double-blind, placebo-controlled, dose-ranging trial of olsalazine for mild-moderately active ulcerative colitis	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Hanauer (1998)	Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: A dose-ranging study.	No outcomes in protocol reported.
Hanauer (2007)	Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial	Outcome could not be extracted from the study as remission with response was reported, but not remission alone. Info: 'Remission' could not be extracted from 'clinical remission or response'.
Hartmann (2010)	Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis	Preparation not available in the UK.

Short Title	Title	Reasons for exclusion
Hiwatashi (2011)	Clinical trial: Effects of an oral preparation of mesalazine at 4 g/day on moderately active ulcerative colitis. A phase III parallel-dosing study	RCT that did not contain a relevant comparison, as both arms were categorised as standard-dose oral aminosalicylates.
Jewell (1974)	Azathioprine in Ulcerative-Colitis - Final Report on Controlled Therapeutic Trial	Population not included in evidence review: population had severe relapse requiring intravenous therapy.
Jiang (2004)	Different therapy for different types of ulcerative colitis in China	RCT that did not contain a relevant comparison, as both arms were categorised as standard-dose oral aminosalicylates.
Kruis (2009)	Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial	RCT that did not contain a relevant comparison, as both arms were categorised as standard-dose oral aminosalicylates.
Lamet (2005)	Efficacy and safety of mesalamine 1 g HS versus 500 mg BID suppositories in mild to moderate ulcerative proctitis: a multicenter randomized study	Comparison not included. Info Both arms of trial compared same dose of topical mesalazine, but different prescription (1g versus 500mg twice a day).
Lamet (2011)	A multicenter, randomized study to evaluate the efficacy and safety of mesalamine suppositories 1 g at bedtime and 500 mg Twice daily in patients with active mild-to-moderate ulcerative proctitis	Comparison not included. Info: Both arms of trial compared same dose of topical mesalazine, but different prescription (1g versus 500mg twice a day).
Lee (1996)	A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis	Severity of the population included was not described.
Lemann (1995)	Comparison of Budesonide and 5-Aminosalicylic Acid Enemas in Active Distal Ulcerative-Colitis	Severity of the population included was not described.
Lindgren (2002)	Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis	RCT that did not contain a relevant comparison, as both arms were categorised as topical (liquid enema) budesonide.
Lofberg (1994)	Budesonide versus prednisolone retention enemas in active distal ulcerative colitis.[Erratum appears in Aliment Pharmacol Ther 1995 Apr;9(2):213]	No outcomes in protocol reported. Preparation not available in the UK.

Short Title	Title	Reasons for exclusion
Marakhouski (2005)	A double-blind dose-escalating trial comparing novel mesalazine pellets with mesalazine tablets in active ulcerative colitis.[Erratum appears in Aliment Pharmacol Ther. 2005 Mar 15;21(6):793]	Comparison not included. Info: Comparison of different preparations (pellets versus tablets) of same dose of oral mesalazine.
Meyers (1987)	Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulfasalazine. A prospective, randomized, placebo-controlled, double-blind, dose-ranging clinical trial	No outcomes in protocol reported.
Miglioli (1989)	Oral 5-ASA (Asacol) in mild ulcerative colitis. A randomized double blind dose ranging trial	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Mulder (1988)	Double-blind comparison of slow-release 5-aminosalicylate and sulfasalazine in remission maintenance in ulcerative colitis	Ulcerative colitis in remission phase.
Ogata (2006)	A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis.[Erratum appears in Gut. 2006 Nov;55(11):1684 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected; Dosage error in article text]	>10% of study population had severe ulcerative colitis.
Ogata (2012)	Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroidrefractory ulcerative colitis.	Proportion with severe UC not reported.
Oren (1996)	Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial	Chronic active ulcerative colitis.
Porro (1994)	Comparative trial of methylprednisolone and budesonide enemas in active distal ulcerative colitis	Outcome (remission) could not be included as it was not defined.
Powell-Tuck (1978)	A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis	Comparison not included.
Powell-Tuck (1986)	A Defense of the Small Clinical-Trial - Evaluation of 3 Gastroenterological Studies	Systematic or narrative review: used to identify relevant references.
Prantera (2005)	A new oral delivery system for 5-ASA: Preliminary clinical findings for MMx	Preparation not available in the UK.
Raedler (2004)	Mesalazine (5-aminosalicylic acid) micropellets show similar efficacy and tolerability to mesalazine tablets in patients with ulcerative colitis--results from a randomized-controlled trial.	Comparison not included. Info: Comparison of same dose of ASA, different preparations.
Rijk (1991)	The efficacy and safety of sulphasalazine and olsalazine in patients with active ulcerative colitis	Abstract; protocol; conference proceeding or

Short Title	Title	Reasons for exclusion
		non-peer reviewed publication.
Rizzello (2001)	Oral beclomethasone dipropionate in patients with mild to moderate ulcerative colitis: a dose-finding study.	RCT that did not contain a relevant comparison, as beclomethasone doses above 5mg was not included.
Robinson (1988)	Olsalazine in the treatment of mild to moderate ulcerative colitis	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Romano (2010)	Oral beclomethasone dipropionate in pediatric active ulcerative colitis: a comparison trial with mesalazine	Beclometasone excluded in paediatric population.
Schroeder (1987)	Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative-Colitis - A Randomized Study	Extent of disease was not reported.
Selby (1985)	Olsalazine in active ulcerative colitis	Outcome(s) could not be analysed (no events were reported).
Shivananda (1996)	Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD).	Systematic or narrative review: used to identify relevant references.
Sood (2002)	The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis	Ulcerative colitis in remission phase.
Sood (2002)	Methylprednisolone acetate versus oral prednisolone in moderately active ulcerative colitis	Route of administration (intramuscular/intravenous) not included.
Tarpila (1994)	Budesonide enema in active haemorrhagic proctitis--a controlled trial against hydrocortisone foam enema	Preparation not available in the UK.
van Bodegraven (1996)	Distribution of mesalazine enemas in active and quiescent ulcerative colitis	No outcomes in protocol reported.
Williams (1987)	Double-Blind, Placebo-Controlled Evaluation of 5-Asa Suppositories in Active Distal Proctitis and Measurement of Extent of Spread Using Tc-99M-Labeled 5-Asa Suppositories	No outcomes in protocol reported.
Willoughby (1986)	5-Aminosalicylic acid (Pentasa) in enema form for the treatment of active ulcerative colitis	No outcomes in protocol reported.
Zinberg (1990)	Double-Blind Placebo-Controlled Study of Olsalazine in the Treatment of Ulcerative-Colitis	No outcomes in protocol reported. Info: It is unclear if the discontinuations reported are attributed to

Short Title	Title	Reasons for exclusion
		disease worsening or drug adverse effects.

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3 **Excluded studies from 2019 guideline update**
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Short Title	Title	New column
Akobeng (2016)	Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease	Ulcerative colitis in remission phase.
Assche (2015)	Erratum: oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study (American Journal of Gastroenterology (2015) 110 (708-715) DOI: 10.1038/ajg.2015.114)	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Assche (2015)	Oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study	Intervention not available in the UK. Info: Beclometasone "clipper" tablets not available in the UK.
Balzola (2013)	Randomised clinical trial: Once- Vs. twice-daily prolonged-release mesalazine for active ulcerative colitis	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Chande (2014)	Methotrexate for induction of remission in ulcerative colitis	Systematic or narrative review: used to identify relevant references.
Chen (2015)	Pentasa enema may be superior to salofalk or glucocorticoid in patients with left-sided active ulcerative colitis	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Crispino (2015)	Efficacy of mesalazine or beclomethasone dipropionate enema or their combination in patients with distal active ulcerative colitis	Intervention not available in the UK.
Cuffari (2016)	Randomized clinical trial: pharmacokinetics and safety of multimatrix mesalamine for treatment of pediatric ulcerative colitis	Pharmacokinetic study.
D'Haens (2017)	Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis	Comparison not included.
Dhaka (2016)	Randomized controlled trial comparing the efficacy of measalamine and oral steroids in patients with moderately active ulcerative colitis	Abstract; protocol; conference proceeding or non-peer reviewed publication.

Short Title	Title	New column
Flourié (2013)	Randomised clinical trial: once- vs. twice-daily prolonged-release mesalazine for active ulcerative colitis	Comparison not included.
Ford (2012)	Efficacy of oral vs topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis (Structured abstract)	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Hindryckx (2017)	Biologic drugs for induction and maintenance of remission in Crohn's disease: a network meta-analysis	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Kawakami (2015)	Effects of oral tacrolimus as a rapid induction therapy in ulcerative colitis	Observational study design.
Komaki (2016)	Efficacy and Safety of Tacrolimus Therapy for Active Ulcerative Colitis; A Systematic Review and Meta-analysis	Systematic or narrative review: used to identify relevant references.
Kruis (1998)	Olsalazine versus mesalazine in the treatment of mild to moderate ulcerative colitis	Intervention not available in the UK. Info: Mesalamine 'Claversal'.
Lasa (2017)	Efficacy of Tacrolimus for Induction of Remission in Patients with Moderate-to-Severe Ulcerative Colitis: A Systematic Review and Meta-Analysis	Systematic or narrative review: used to identify relevant references.
Lie (2014)	Drug therapies for ulcerative proctitis: systematic review and meta-analysis	Systematic or narrative review: used to identify relevant references.
Manguso (2016)	Efficacy and Safety of Oral Beclomethasone Dipropionate in Ulcerative Colitis: A Systematic Review and Meta-Analysis	Systematic or narrative review: used to identify relevant references.
Mate-Jimenez (2000)	6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease	Comparison not included. Trial duration longer than 12 weeks, no results reported for up to 12 weeks.
Nguyen (2013)	Erratum: 5-aminosalicylic acid is not protective against colorectal cancer in inflammatory bowel disease: A meta-analysis of non-referral populations (American Journal of Gastroenterology (2012) 107 (1298-1304) DOI:10.1038/ajg.2012.198)	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Pica (2013)	Oral beclomethasone dipropionate vs 5-ASA enema in active UC: lower efficacy but better compliance	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Pica (2015)	A randomized trial comparing 4.8 vs. 2.4 g/day of oral mesalazine for maintenance of remission in ulcerative colitis	Ulcerative colitis in remission phase.

Short Title	Title	New column
Raskin (2014)	Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials	Population not included.
Rubin (2016)	Ulcerative Colitis Remission Status After Induction With Mesalazine Predicts Maintenance Outcomes: the MOMENTUM Trial	Ulcerative colitis in remission phase.
Sun (2016)	Mesalazine Modified-Release Tablet in the Treatment of Ulcerative Colitis in the Remission Phase: A Chinese, Multicenter, Single-Blind, Randomized Controlled Study	Ulcerative colitis in remission phase.
Turner (2016)	Once versus twice daily mesalazine to induce remission in pediatric ulcerative colitis: an investigator-initiated randomized controlled trial	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Turner (2017)	Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial	Comparison not included.
Van Assche (2015)	Corrigendum: Oral Prolonged Release Beclomethasone Dipropionate and Prednisone in the Treatment of Active Ulcerative Colitis: Results From a Double-Blind, Randomized, Parallel Group Study.[Erratum for Am J Gastroenterol. 2015 May;110(5):708-15; PMID: 25869389]	Abstract; protocol; conference proceeding or non-peer reviewed publication.
Wang (2016)	Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis	Systematic or narrative review: used to identify relevant references.
Wang (2016)	Efficacy of single vs multiple doses of 5-aminosalicylic acid (5-ASA) in the treatment of mild-moderate ulcerative colitis: An open randomized clinical trial	Comparison not included.
Zeng (2017)	Budesonide foam for mild to moderate distal ulcerative colitis: A systematic review and meta-analysis	Systematic or narrative review: used to identify relevant references.
Zhao (2016)	Efficacy and Safety of Beclomethasone Dipropionate versus 5-Aminosalicylic Acid in the Treatment of Ulcerative Colitis: A Systematic Review and Meta-Analysis	Systematic or narrative review: used to identify relevant references.
Zhao (2017)	Efficacy and safety of rectal 5-aminosalicylic acid versus corticosteroids in active distal ulcerative colitis: a systematic review and network meta-analysis	Systematic or narrative review: used to identify relevant references.
Zhu (2012)	Can oral 5-aminosalicylic acid be administered once daily in the treatment of mild-to-moderate ulcerative colitis? A meta-analysis of randomized-controlled trials	Comparison not included.

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2 **Excluded studies from 2019 guideline update top-up search**

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Short Title	Title	Exclusion reason
Chande (2014)	Methotrexate for induction of remission in ulcerative colitis	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
D'Haens (2017)	Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis	Comparison not included in evidence review.
Dignass (2018)	Efficacy and safety of a novel high-dose mesalazine tablet in mild to moderate active ulcerative colitis: a double-blind, multicentre, randomised trial	Comparison not included in evidence review.
Kato (2018)	Comparison of rectal and oral mesalazine for treatment of rectal ulcerative proctitis: a prospective randomised clinical trial (CORRECT study)	Abstract
Kokkinidis (2017)	Emerging treatments for ulcerative colitis: a systematic review	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Komaki (2017)	Pharmacologic therapies for severe steroid refractory hospitalized ulcerative colitis: A network meta-analysis	Population not included - severe ulcerative colitis.
Kreijne (2018)	Tacrolimus suppositories as induction therapy for refractory ulcerative proctitis: a randomised controlled trial	Abstract
Lasa (2018)	Efficacy and safety of anti-integrin antibodies in inflammatory bowel disease: Systematic review and meta-analysis	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Lawrance (2017)	Efficacy of Rectal Tacrolimus for Induction Therapy in Patients With Resistant Ulcerative Proctitis	Included in evidence review.
Loftus (2018)	Sustained corticosteroid-free remission with vedolizumab in moderate-to-severe ulcerative colitis: a post hoc analysis of GEMINI 1	Abstract
Fang (2018)	Mesalazine combined with golden bifid for treatment of patients with ulcerative colitis: effect on inflammatory response and anorectal motility	Not in English.
Perez-Calle (2016)	Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulce-rative colitis	Included in evidence review. Secondary publication of included study.
Roblin (2018)	Interest in the addition of azathioprine (AZA) to the switch of anti-TNF in IBD patients in loss of response with undetectable anti-TNF trough levels and anti-drug antibodies: a prospective randomised trial	Abstract, Indirect population - not post-surgery.
Rubin (2017)	Budesonide Multimatrix Is Efficacious for Mesalamine-refractory, Mild to Moderate	Included in evidence review.

Short Title	Title	Exclusion reason
	Ulcerative Colitis: A Randomised, Placebo-controlled Trial	
Sherlock (2015)	Oral budesonide for induction of remission in ulcerative colitis	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.
Simadibrata (2017)	Efficacy of Curcumin as Adjuvant Therapy to Induce or Maintain Remission in Ulcerative Colitis Patients: an Evidence-based Clinical Review	Intervention not included in evidence review.
Turner (2016)	Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial	Comparison not included in evidence review.
Turner (2017)	Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial	Abstract
van Gennep (2017)	Thiopurine Treatment in Ulcerative Colitis: A Critical Review of the Evidence for Current Clinical Practice	Systematic review/meta-analysis which does not meet criteria of protocol. Relevant references were checked.

Appendix N: Research recommendations

Question	In mild-to-moderate first presentation or inflammatory exacerbation of proctitis that is resistant to standard treatment, what is the effectiveness of topical immunomodulators, such as tacrolimus, in achieving clinical remission and what is the most effective formulation (suppository/ointment)?
Population	People with first presentation, or exacerbation, of chronic proctitis who have received standard treatment but still have active disease.
Intervention	Topical immunomodulator (ointment or suppository).
Comparator	Placebo, other treatment, other formulation/dose.
Outcomes	• Clinical remission • Endoscopic remission • Adverse outcomes • Withdrawal due to adverse events • Quality of life
Study design	Randomised Controlled Trial
Potential criterion	**Explanation**
Importance to patients, service users or the population	If shown to be effective and cost-effective, immunomodulators could provide another treatment option when standard treatments have failed to induce remission. This would improve outcomes and quality of life for people whose proctitis did not respond to standard treatments.
Relevance to NICE guidance	The committee agreed not to recommend topical tacrolimus or other topical immunomodulators since the evidence was unclear about their effectiveness in achieving clinical remission in first presentation or inflammatory exacerbation of proctitis that is resistant to standard treatment. Additionally, the committee noted that it is unclear which formulation of topical immunomodulator (suppository or ointment) is more clinically effective in practice – it was sceptical that ointment would ever be used.
Current evidence base	The evidence considered for tacrolimus came from one small RCT of 20 participants which compared tacrolimus and placebo. It was of low quality and may not be directly appropriate to a UK population. No evidence was included for other immunomodulators.
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people with resistant proctitis that this study is feasible.

Question	What is the effectiveness of oral tacrolimus and systemic (intramuscular/subcutaneous/oral) methotrexate in the induction of remission in mild-to-moderate ulcerative colitis unresponsive to aminosalicylates?
Population	People with first presentation, or exacerbation, of mild-moderate ulcerative colitis who have been unresponsive to aminosalicylate treatment and still have active disease.
Intervention	Tacrolimus (oral) or methotrexate (oral, intramuscular or subcutaneous).
Comparator	Placebo, other treatment, other formulation/dose.
Outcomes	• Clinical remission • Endoscopic remission • Adverse outcomes • Withdrawal due to adverse events • Quality of life
Study design	Randomised Controlled Trial
Potential criterion	**Explanation**
Importance to patients, service users or the population	If shown to be effective and cost-effective, immunomodulators could provide another treatment option when standard aminosalicylate treatment has failed to induce remission. This would improve outcomes and quality of life for people whose ulcerative colitis did not respond to aminosalicylates.
Relevance to NICE guidance	The committee agreed not to recommend topical tacrolimus or methotrexate since the evidence was unclear about their effectiveness in achieving clinical remission in first presentation or inflammatory exacerbation of ulcerative colitis that is resistant to aminosalicylate treatment. Additionally, the committee noted that it is unclear which formulation of methotrexate (oral or injection) is more clinically effective in practice.
Current evidence base	The evidence considered for tacrolimus came from one small RCT of 20 participants which compared topical tacrolimus and placebo. It was of low quality and may not be directly appropriate to a UK population. No evidence was seen for methotrexate
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people with resistant ulcerative colitis that this study is feasible.

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Question	What is the clinical and cost effectiveness of oral prednisolone, budesonide, beclometasone in addition to aminosalicylates compared with each other and with aminosalicylate monotherapy for the induction of remission for people with mild-to-moderate ulcerative colitis?
Population	People with first presentation or acute exacerbation of mild-moderate ulcerative colitis
Intervention	Aminosalicylate plus oral corticosteroid (prednisolone, budesonide or beclometasone)
Comparator	Aminosalicylate alone or in combination with other corticosteroid/dose
Outcomes	• Clinical remission • Endoscopic remission • Adverse events • Withdrawal due to adverse events • Quality of life
Study design	Randomised Controlled Trial
Potential criterion	**Explanation**
Importance to patients, service users or the population	It is unclear from the evidence whether all corticosteroids are equally useful in combination with aminosalicylate therapy for inducing remission in mild-moderate ulcerative colitis. It is important to know what corticosteroids are effective (if any) so that patients can receive the best treatment with the least side-effects.
Relevance to NICE guidance	The committee recognised the limited evidence base for oral corticosteroids and noted the uncertainty about which oral corticosteroid is most clinically and cost effective in all extents of disease, but in particular in proctosigmoiditis, left-sided and extensive disease.
Current evidence base	Only one study allowed direct comparison of different corticosteroids (both topical).
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people

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