

# Ulcerative colitis

Management in adults, children and young people

*Clinical guideline*

*Methods, evidence and recommendations*

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*Final version*

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Health and Care Excellence*



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# 1 Introduction

Ulcerative colitis is the most common type of inflammatory disease of the bowel. It has an incidence in the UK of approximately 10 per 100,000 people annually,<sup>184,185,201</sup> and a prevalence of approximately 240 per 100,000.<sup>184</sup> This amounts to around 146,000 people in the UK with a diagnosis of ulcerative colitis. The cause of ulcerative colitis is unknown. It can develop at any age, but peak incidence is between the ages of 15 and 25 years, with a second, smaller peak between 55 and 65 years (although this second peak has not been universally demonstrated).<sup>130</sup> The British Paediatric Surveillance Unit reported an incidence of ulcerative colitis in children aged younger than 16 years in the United Kingdom, of 1.4 per 100,000 with a greater proportion of Asian children having ulcerative colitis than other children.<sup>192</sup> The median age for diagnosis of ulcerative colitis overall in this childhood cohort was 11.7 years (range 9.3 to 13.7 years).

Ulcerative colitis usually affects the rectum, and a variable extent of the colon proximal to the rectum. The inflammation is continuous in extent. Inflammation of the rectum is referred to as proctitis, and inflammation of the rectum and sigmoid as proctosigmoiditis. Left-sided colitis refers to disease involving the colon distal to the splenic flexure. Extensive colitis affects the colon proximal to the splenic flexure, and includes pan-colitis, where the whole colon is involved.

Symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defaecate and abdominal pain.

Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled. Typically, it has a relapsing–remitting pattern. An estimated 50% of people with ulcerative colitis will have at least one relapse per year.<sup>146</sup> About 80% of these are mild to moderate and about 20% are severe.<sup>212</sup>

The Truelove and Witts' criteria are outlined in Table 6. These are simple clinical and laboratory measures and are widely used in clinical practice to guide treatment. In addition, a number of laboratory, endoscopic and radiological features may reflect the severity of an attack, and have been assessed in terms of their ability to predict the need for colectomy (see section 5.48). These include measurements of C-reactive protein, colonic dilatation or the presence of colonic mucosal islands on a plain abdominal X-ray and deep ulceration on endoscopic assessment. The Truelove and Witts' criteria were used as a definition of the severity of an attack on the basis of their widespread use and ease of applicability to clinical practice. The use of clinical scoring systems was a way of predicting the response to medical treatment, and the need for surgery was assessed in section 5.48.

Approximately 25% of people with ulcerative colitis will have one or more episodes of acute severe colitis in their lifetime, with a 29% colectomy rate.<sup>212</sup> Although mortality rates have improved steadily over the past 30 years, acute severe colitis still has a mortality rate of up to 2%. Mortality is directly influenced by the timing of interventions, including medical therapy and colectomy. The most recent UK audit demonstrated an overall UK national mortality of 0.8%.

Current medical approaches focus on treating active disease to address symptoms of urgency, frequency of defaecation and rectal bleeding, and also to improve quality of life, and thereafter to maintain remission. The long-term benefits of achieving mucosal healing remain unclear. The treatment chosen for active disease is likely to depend on clinical severity, extent of disease and the person's preference, and may include the use of aminosalicylates, corticosteroids or biological drugs. These drugs can be oral or topical (into the rectum), and corticosteroids may be administered intravenously in people with acute severe disease. Surgery may be considered as emergency treatment for severe ulcerative colitis that does not respond to drug treatment. People may also choose to have elective surgery for unresponsive or frequently relapsing disease that is affecting their quality of life.

If an episode of acute severe colitis does not respond to standard first-line management with intravenous corticosteroids, 'rescue' therapy with intravenous ciclosporin or infliximab may be required - though the most recent, third round, of the UK national IBD audit, described only 16.8% of patients who do not respond to intravenous steroids receiving anti-TNF therapy and 23% receiving ciclosporin.<sup>221</sup> The use of infliximab in this situation is outlined in NICE TA 163.<sup>149</sup> Response rate is variable -reported as 85% to anti-TNF agents and 64% to ciclosporin in the third round of the UK IBD audit.<sup>221</sup>

Most patients receive maintenance therapy with aminosalicylates. There may be variation in the doses of aminosalicylates and in whether a combination of treatment routes is used. Regarding immunosuppressive azathioprine or mercaptopurine, it appears that azathioprine and mercaptopurine are increasingly used to maintain remission in people with frequently-relapsing ulcerative colitis.

Elective surgery, in the form of pan-proctocolectomy, with formation of an ileoanal pouch or ileostomy, can be an effective treatment for eliminating the symptoms of ulcerative colitis where these symptoms are refractory to treatment or rapidly and frequently recur. However postoperative morbidity is associated with both a stoma and ileoanal pouch. Complications of pan-proctocolectomy may include: decrease in female fertility, male impotency, pouchitis and small bowel obstruction. Problems with urgency, leakage and nocturnal soiling may persist after surgery, and some patients may need a permanent ileostomy if ileal pouch anastomosis fails. Even in expert centres, pan-proctocolectomy has an operative mortality of between 1 and 4%, and postoperative lifelong morbidity of up to 15%.

Ulcerative colitis has a well-documented association with the development of colorectal cancer, with greatest risk in people with long-standing and extensive disease. The overall lifetime risk of colorectal cancer in people with ulcerative colitis is approximately 2.7%, with an annual incidence of dysplasia or cancer of between 3.7 and 5.7%. Moreover, the degree of colonic inflammation is a predictor of dysplasia or cancer development. This emphasises the importance of adequate and effective control of disease activity to reduce the risk of colorectal cancer. The approach to surveillance of people with ulcerative colitis for dysplasia or cancer is described in NICE clinical guideline 118.<sup>152</sup>

Advice and support for people with ulcerative colitis is important, in terms of discussing the effects of the condition and its course, medical treatment options, the effects of medication and the monitoring required. Around 10% of inpatients with inflammatory bowel disease reported a lack of information about drug side effects on discharge from hospital.<sup>220</sup> Information to support decisions about surgery is also essential, both for clinicians and for people facing the possibility of surgery. This includes recognising adverse prognostic factors for people admitted with acute severe colitis to enable timely decisions about escalating medical therapy or predicting the need for surgery. It is also very important to provide relevant information to support people considering elective surgery.

The third round of the National IBD audit provided some evidence of variation in practice, including whether patients are admitted to a specialist gastroenterology ward, access to nurse specialist advice, prescription of bone protection for patients discharged on systemic corticosteroids and length of stay for admitted patients.<sup>220</sup> A record of the paediatric ulcerative colitis activity index was recorded in 20% of admitted paediatric patients.<sup>222</sup>

The wide choice of drug preparations and dosing regimens, the judgement required in determining the optimum timing for surgery (both electively and as an emergency) and the importance of support and information may lead to variation in practice across the UK. This guideline aims to address this variation, and to help healthcare professionals to provide consistent high-quality care. Managing ulcerative colitis in adults, children and young people overlaps in many regards, so the guideline incorporates advice that is applicable to children and young people. This again should help to address potential inconsistencies in practice.

Care of people with ulcerative colitis is usually shared between primary care and specialist gastroenterology units working in collaboration with specialist colorectal surgical units. Close links are required to allow specialist input, rapid access to advice (especially when symptoms worsen) and coordinated monitoring of drug-side effects, and to ensure that associated issues (such as monitoring of bone density) are addressed. However, the number of adults with ulcerative colitis definitely under specialist care may not be as high as thought, and may be as low as 30%.<sup>184</sup> The most appropriate setting for a person's care is likely to come under increasing scrutiny as commissioning groups seek to provide more care in the community.

This guideline therefore covers areas defined within the scope (Appendix A). Detailed delineation of areas excluded is given in the scope, but it should be noted that this guideline does not address areas of diagnosis, diagnostic investigation and surgical technique. Chapter 5 deals with induction of remission - the treatment of patients with active disease in relapse. This includes disease of limited extent (proctitis and proctosigmoiditis) and more extensive ulcerative colitis and includes treatment of acute severe colitis. In association with this, assessment of patients with acute severe colitis and their risk of requiring surgery or escalation of therapy are considered. Following this, drug treatment to maintain remission is examined and then considerations of information for people considering elective surgery, considerations of pregnancy in women with ulcerative colitis and bone health and growth and development in children.



## 2 Development of the guideline

### 2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- information for the public is written using suitable language for people without specialist medical knowledge
- the NICE pathway brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at [www.nice.org.uk](http://www.nice.org.uk)

### 2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

To produce a clinical guideline on the management of ulcerative colitis.

## 2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Alan Lobo in accordance with guidance from the National Institute for Health and Care Excellence (NICE).

The group met every six weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

## 2.4 What this guideline covers

Groups covered by this guideline are adults, children and young people with a diagnosis of ulcerative colitis. Consideration is given to specific needs, if any, of:

- children and young people (including transition between paediatric and adult services and puberty)
- pregnant women.

Key clinical issues covered:

- Drug therapy for the induction of remission for mild, moderate and severe active ulcerative colitis, and maintenance of remission, including the following drug categories:
  - o aminosalicylates
  - o corticosteroids
  - o immunomodulators – azathioprine, mercaptopurine, methotrexate, ciclosporin and tacrolimus.

Guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

- Indications and timing of surgical management, specifically, ileoanal pouch surgery or total colectomy for acute severe colitis, recurrent relapses or continuous uncontrolled symptoms.
- Monitoring of bone health.
- Monitoring of growth in children.
- Information, education and support for people with ulcerative colitis and their families and carers.

For further details please refer to the scope in Appendix A and review questions in Appendix C.

## 2.5 What this guideline does not cover

Groups not covered by this guideline are people with indeterminate colitis.

Key clinical issues not covered:

- Diagnosis.
- Treatment of extraintestinal manifestations of ulcerative colitis.
- Surgical techniques (except those listed above).
- Reconstruction after previous surgery.
- Pouchitis.
- Management with:
  - o antibiotics
  - o fish oil
  - o helminths
  - o heparin as a primary treatment
  - o leukapheresis
  - o nicotine
  - o probiotics.

## 2.6 Relationships between the guideline and other NICE guidance

### Related NICE Technology Appraisal Guidance:

- Adalimumab for the treatment of moderate to severe ulcerative colitis (terminated appraisal). NICE technology appraisal guidance 262 (2012). Available from [www.nice.org.uk/guidance/TA262](http://www.nice.org.uk/guidance/TA262)
- Infliximab for acute exacerbations of ulcerative colitis. NICE technology appraisal guidance 163 (2008). Available from [www.nice.org.uk/guidance/TA163](http://www.nice.org.uk/guidance/TA163)
- Infliximab for subacute manifestations of ulcerative colitis. NICE technology appraisal guidance 140 (2008). Available from [www.nice.org.uk/guidance/TA140](http://www.nice.org.uk/guidance/TA140)

### Related NICE Interventional Procedure Guidance:

- Injectable bulking agents for faecal incontinence. NICE interventional procedure guidance 210 (2007). Available from [www.nice.org.uk/guidance/IPG210](http://www.nice.org.uk/guidance/IPG210)
- Leukapheresis for inflammatory bowel disease. NICE interventional procedure guidance 126 (2005). Available from [www.nice.org.uk/guidance/IPG126](http://www.nice.org.uk/guidance/IPG126)

### Related NICE Clinical Guidelines:

- Fertility (update). NICE clinical guideline 156 (2013). Available from [www.nice.org.uk/guidance/CG156](http://www.nice.org.uk/guidance/CG156)
- Crohn's disease. NICE clinical guideline 152 (2012). Available from [www.nice.org.uk/guidance/CG152](http://www.nice.org.uk/guidance/CG152)
- Osteoporosis: assessing the risk of fragility fracture. NICE clinical guideline 146 (2012). Available from [www.nice.org.uk/guidance/CG146](http://www.nice.org.uk/guidance/CG146)
- Patient experience in adult NHS services. NICE clinical guidance 138 (2012). Available from [www.nice.org.uk/guidance/CG138](http://www.nice.org.uk/guidance/CG138)

- Colorectal cancer. NICE clinical guideline 131 (2011). Available from [www.nice.org.uk/guidance/CG131](http://www.nice.org.uk/guidance/CG131)
- Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. NICE clinical guideline 118 (2011). Available from [www.nice.org.uk/guidance/CG118](http://www.nice.org.uk/guidance/CG118)
- Medicines adherence. NICE clinical guideline 76 (2009). Available from [www.nice.org.uk/guidance/CG76](http://www.nice.org.uk/guidance/CG76)
- Irritable bowel syndrome in adults. NICE clinical guideline 61 (2008). Available from [www.nice.org.uk/guidance/CG61](http://www.nice.org.uk/guidance/CG61)
- Faecal incontinence. NICE clinical guidance 49 (2007). Available from [www.nice.org.uk/guidance/CG49](http://www.nice.org.uk/guidance/CG49)
- Nutrition support in adults. NICE clinical guideline 32 (2006). Available from [www.nice.org.uk/guidance/CG32](http://www.nice.org.uk/guidance/CG32)
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Available from [www.nice.org.uk/guidance/CG27](http://www.nice.org.uk/guidance/CG27)

## 3 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009<sup>151</sup>.

### 3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The GDG chose approximately 7 outcomes identifying which outcomes were critical to their decision making and which were important. This distinction helped the GDG to make judgements about the importance of the different outcomes and their impact on decision making. For example, mortality will usually be considered a critical outcome and would be given greater weight when considering the clinical effectiveness of an intervention than an important outcome with less serious consequences. The GDG decide on the relative importance in the review protocol before seeing the review. The questions were based on the key clinical issues identified in the scope (Appendix A).

A total of 8 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Chapter	Type of review	Review question	Outcomes
5	Intervention	In adults, children and young people with mild to moderate ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates and immunomodulators (mercaptopurine, azathioprine, methotrexate and tacrolimus) for the induction of remission compared to themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?	<u>Critical outcomes</u> Clinical remission Clinical improvement Health related quality of life <u>Important outcomes</u> Endoscopic remission Clinical and endoscopic remission Adverse events Serious adverse events Colectomy Hospitalisations.
5	Intervention	In adults, children and young people with acute severe ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids and ciclosporin compared to each other and their combination (corticosteroids and ciclosporin) for the induction of remission?	<u>Critical outcomes</u> Clinical remission Clinical improvement Health related quality of life Mortality <u>Important outcomes</u> Endoscopic remission Clinical and endoscopic remission

Chapter	Type of review	Review question	Outcomes
			Adverse events Serious adverse events Colectomy Hospitalisations.
5	Prognostic	Which validated tools are the most predictive of the likelihood of surgery in people with acute severe ulcerative colitis?	Statistical measures of discrimination and calibration including Area Under the Curve (AUC).
6	Observational and qualitative	For adults, children and young people with ulcerative colitis considering surgery, what information on short and long term outcomes should be offered to patients and their carers by healthcare professionals?	Any outcomes that are identified by the participants in the studies. This will be broken down into: <ul style="list-style-type: none"> <li>• Short term outcomes (biological, physical/interference with daily activities, psychological)</li> <li>• Long term outcomes (biological, physical/interference with daily activities, psychological).</li> </ul>
7	Intervention	In adults, children and young people with ulcerative colitis in remission, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates, immunomodulators (mercaptopurine, azathioprine, methotrexate and tacrolimus) for the maintenance of remission compared to themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?	<u>Critical outcomes</u> Relapse Health related quality of life <u>Important outcomes</u> Adverse events Serious adverse events Colectomy Hospitalisations.
8	Observational	What are the consequences of using drug treatments for the induction and maintenance of remission in pregnant women?	In addition to the questions for induction and maintenance these outcomes were included. <u>Critical outcomes</u> Stillbirth Congenital abnormalities Spontaneous abortion Premature births (<37 weeks gestation) Low birth weight (<2.5kg)

Chapter	Type of review	Review question	Outcomes
			Maternal mortality <u>Important outcomes</u> Normal birth (≥37 weeks, live birth with no abnormalities) Health related quality of life.
9	Prognostic	In children and young people with ulcerative colitis, are disease activity, systemic corticosteroid use, total vitamin D and malnutrition, risk factors for poor bone health?	<u>Critical outcomes</u> Incidence of fractures Osteoporosis /osteopenia as indicated by bone mineral density z score Reduction in bone mineral density score <u>Important outcomes</u> Epiphyseal fusion Bone age (wrist x-rays).
9	Observational	In children and young people with ulcerative colitis, what are the optimal strategies (timing, location) for monitoring growth?	<u>Critical outcomes</u> Deviation from normal/baseline linear height (growth velocity) as measured on the centile chart trajectory. Deviation from Tanner staging (pubertal development). Bone age (wrist x-rays) <u>Important outcomes</u> Deviation from normal weight as measured on the centile weight trajectory.

## 3.2 Searching for evidence

### 3.2.1 Clinical literature search

The aim of the literature search was to identify all available, relevant published evidence in relation to the key clinical questions generated by the GDG. Systematic literature searches were undertaken to identify evidence within the published literature in order to answer the review questions as per The Guidelines Manual [2009].<sup>151</sup> Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in the English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and *The Cochrane Library*. All searches were updated on 15<sup>th</sup> November 2012. No papers published after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies in a specific area. The

questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database ([www.g-i-n.net](http://www.g-i-n.net))
- National Guideline Clearing House ([www.guideline.gov/](http://www.guideline.gov/))
- National Institute for Health and Care Excellence (NICE) ([www.nice.org.uk](http://www.nice.org.uk))
- National Institutes of Health Consensus Development Program ([consensus.nih.gov/](http://consensus.nih.gov/))
- Health Information Resources, NHS Evidence ([www.library.nhs.uk/](http://www.library.nhs.uk/))

The titles and abstracts of records retrieved by the searches were scanned for relevance to the GDG's review questions. Any potentially relevant publications were obtained in full text. These were assessed against the inclusion criteria and the reference lists were scanned for any articles not previously identified. Further references were also suggested by the GDG.

### **3.2.1.1 Call for evidence**

The GDG decided to initiate a 'call for evidence' for the 'what information is needed for people considering surgery' review question as they believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence.

### **3.2.2 Health economic literature search**

Systematic literature searches were also undertaken to identify health economic evidence within the published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the guideline population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in the English language.

The search strategies for health economics are included in Appendix D. All searches were updated on 15<sup>th</sup> November 2012. No papers published after this date were considered.

## **3.3 Evidence of effectiveness**

The evidence was reviewed following the steps shown schematically in Figure 1:

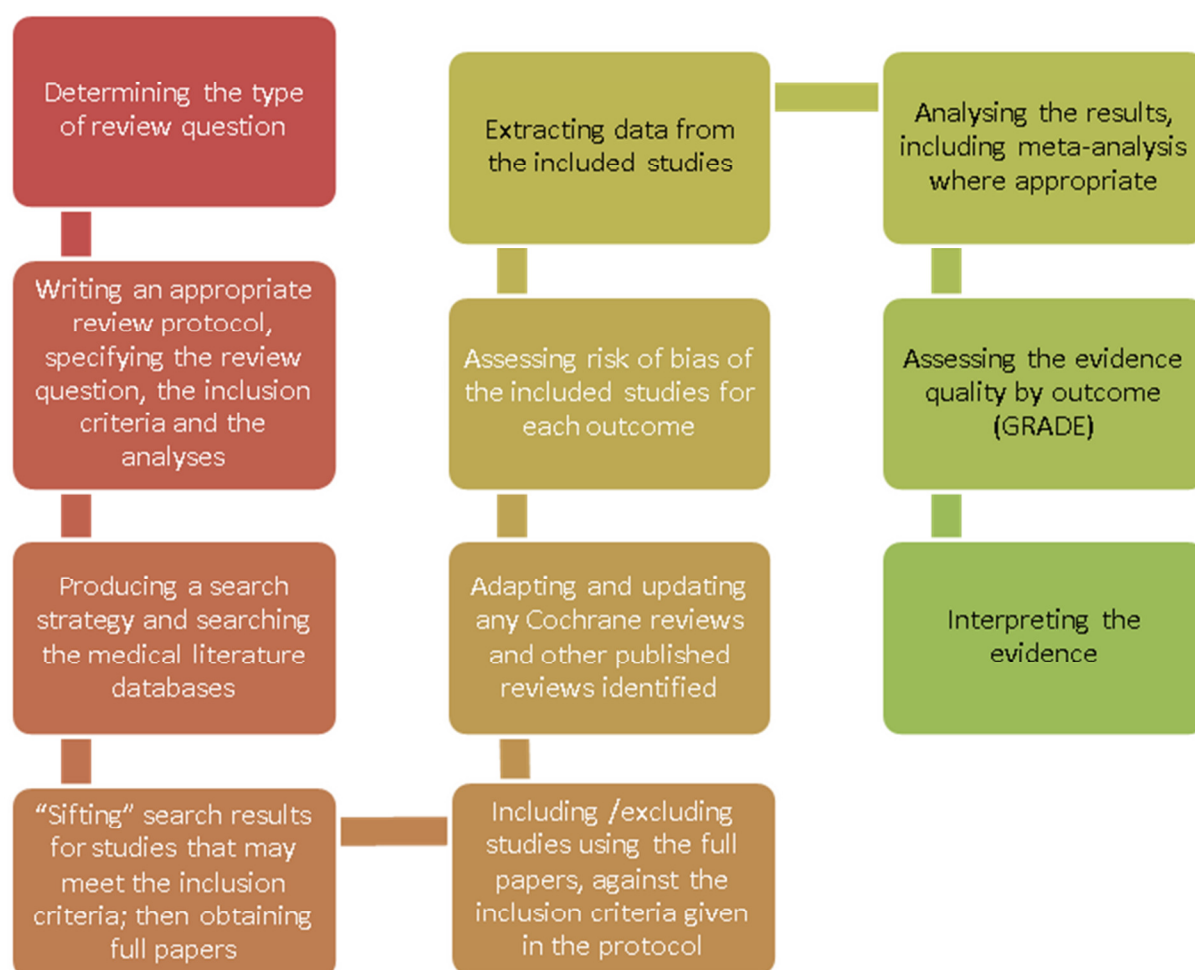
- potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- full papers were reviewed against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- relevant studies were critically appraised using the appropriate checklists as specified in The Guidelines Manual. For prognostic studies, quality was assessed using the checklist for Prognostic studies (NICE Guidelines Manual, 2009).<sup>151</sup>
- key information was extracted on the study's methods and PICO factors and results were presented in evidence tables (Appendix G).



- summaries of the evidence were generated by outcome (included in the relevant chapter write-ups) and were presented in GDG meetings:
  - o Randomised studies: meta-analysed, where appropriate and reported in GRADE profiles
  - o Prognostic studies: assessing risk factors data were presented as a range of values, usually in terms of the relative effect as reported by the authors and where possible reported in the GRADE profile format.
  - o Prognostic studies evaluating risk tools were presented as measures of prognostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarised in Receiver Operating Curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively (given data were reported at the same thresholds). A meta-analysis could not be conducted because the studies reported data at various thresholds.

Twenty percent (20%) of each of the above stages of the reviewing process was quality assured by the second reviewer to eliminate any potential of reviewer bias or error.

**Figure 1: Step-by-step process of review of evidence in the guideline**



### 3.3.1 Inclusion/exclusion

The inclusion/exclusion of studies was based on the review protocols (Appendix C). The GDG were consulted about any uncertainty regarding inclusion/exclusion.

The guideline population was defined to be adults, children and young people with ulcerative colitis. For some review questions, the review population was confined to special groups such as people who are either in remission or with active disease of varying severity or pregnant women.

Randomised trials, non-randomised trials, and observational studies (including prognostic studies) were included in the evidence reviews as appropriate. Laboratory studies (in vivo or in vitro) were excluded.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information. Conference abstracts included in Cochrane reviews were included when they met the review inclusion criteria and authors were not contacted. Literature reviews, letters and editorials, foreign language publications and unpublished studies were excluded.

The review protocols are presented in Appendix C. Excluded studies (with their exclusion reasons) are listed in Appendix F.

### **3.3.2 Methods of combining clinical studies**

#### **Data synthesis for intervention reviews**

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Where studies reported data which could not be analysed by meta-analysis a narrative summary is provided.

Fixed-effects (Mantel-Haenszel) techniques were used to calculate pooled risk ratios (relative risk) for binary outcomes. For continuous outcomes, measures of central tendency (mean) and variation (standard deviation (SD)) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling mean differences, and where the studies had different scales, standardised mean differences were used. A generic inverse variance option in Review Manager was used if any studies reported solely the summary statistics and 95% confidence interval (or standard error) – this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics - p-values or 95% confidence intervals (95% CI); meta-analysis was then undertaken for the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect on these groups of people with ulcerative colitis. For example, stratifying by frequency of relapses and current use of immunomodulators prior to the trial.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at  $p < 0.1$  and the I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out sensitivity analyses. Sensitivity analyses were carried out looking at the subgroups which were pre-specified by the GDG. If the heterogeneity still remained, a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. The hazard ratio can be translated into an absolute difference in the proportion of patients who are event-free at a particular time point, assuming proportional

hazards. This is calculated using GRADEpro software. Absolute risk differences were presented in the GRADE profiles and in a clinical summary of findings tables, for discussion with the GDG.

Network meta-analyses (NMA) were conducted for the review questions in adults on the induction of remission of mild or moderate left-sided or extensive ulcerative colitis and the maintenance of remission after a mild or moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis. This type of analysis simultaneously compared multiple treatments in a single meta-analysis, preserving the randomization of RCTs included in the reviews of direct comparisons. The aim of the NMAs were to include all relevant evidence in order to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy.

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS version 1.4. We used statistical models for fixed and random effects that allowed inclusion of multi arm trials and accounts for the correlation between arms in the trials with any number of trial arms. The model was based on original work from the University of Bristol (<https://www.bris.ac.uk/cobm/research/mpes/mtc.html>). The quality of each NMA was assessed using the NICE checklist, "NICE DSU evidence synthesis of treatment efficacy in decision making: a reviewer's checklist".

Heterogeneity was assessed in the results of the random effects model by using the method described by Dias et al<sup>56</sup> which compares the size of the treatment effect to the extent of between trials variation.

Inconsistency in the networks was tested by comparing any available direct and indirect treatment comparison and testing the null hypothesis that the indirect evidence was not different than the direct evidence on the relative risk ratio scale using the normal distribution; inconsistency was identified if the median estimates (median relative risk ratios) of the direct comparisons were outside the confidence intervals of the relative risk ratios as generated from the NMA output.

There were three main outputs from the NMA: 1) the estimation of log odds and relative risk ratios (ORs, RRs) (with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence, 2) the probability that each treatment was best based on the proportion of Markov chain iterations in which treatment had the highest probability of achieving the outcomes selected in the networks and 3) the ranking of treatments compared to placebo groups (presented as median rank and its 95% credible intervals).

### **Data synthesis for prognostic factor reviews**

Risk factors for poor bone health in children and young people with ulcerative colitis

Odds ratios (ORs), relative risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CI) for the effect of the pre-specified prognostic factors were extracted from the papers. Studies of lower risk of bias were preferred, taking into account the analysis and the study design; in particular, prospective cohort studies that reported multivariable analyses, which included key confounders as identified by the GDG at the protocol stage for that outcome.

The results from the risk factors of poor bone health in children and young people was presented as a narrative due to the lack of published data.

### **Risk tools for predicting the outcome of acute severe ulcerative colitis**

Coupled forest plots of sensitivity and specificity with their 95% confidence intervals across studies (at various thresholds) were produced for each risk tool, using Cochrane Review Manager (RevMan5) software. In order to do that, 2 by 2 tables (the number of true positives, false positives, true

negatives and false negatives) were either directly taken from the study if given or derived from raw data, or were calculated from the set of test accuracy statistics.

To allow comparison between tests, summary ROC curves were generated for each prognostic test from the pairs of sensitivity and specificity calculated from the 2 x 2 tables, selecting one threshold per study. A ROC plot shows true positive rate (i.e. sensitivity) as a function of false positive rate (i.e. 1 – specificity). Data were entered into Review Manager 5 software and ROC curves were fitted using the Moses Littenburg approach.

Area under the ROC curve (AUC) data for each study was also plotted on a graph, for each prognostic test: the AUC describes the overall prognostic accuracy across the full range of thresholds. The GDG agreed on the following criteria for AUC:  $\leq 0.50$  worse than chance; 0.50-0.60 = very poor; 0.61-0.70 = poor; 0.71-0.80 = moderate; 0.81-0.92 = good; 0.91-1.00 = excellent or perfect test.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots, if appropriate (only when there were similar thresholds). A prognostic meta-analysis was not conducted mainly because of the different thresholds across studies and the complexity of the analysis and time and resource constraints of this guideline development.

### **3.3.1 Type of studies**

For most intervention reviews in this guideline, parallel randomised trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Cross over RCTs were not appropriate for estimating the intervention effects for with the induction of remission of ulcerative colitis as their baseline severity of disease level was likely to have changed. Only data from the first intervention people were exposed to were included from randomised crossover studies in the review. For the prognostic review on the risk factors of poor bone health in children and young people, cross-sectional, prospective and retrospective studies were included and for the prognostic review on predicting the outcome of acute severe ulcerative colitis, prospective and retrospective cohort studies were included. Case control studies were not included.

### **3.3.2 Type of analysis**

Estimates of effect from individual studies were based on the author reported data. As a preference available case analysis (ACA) was used and if this was not reported intention to treat analysis (ITT) was then used.

The ACA method is preferred to an intention-to-treat with imputation analysis (ITT), in order to avoid making assumptions about the participants for whom outcome data were not available, and furthermore assuming that those with missing outcome data have the same event rate as those who continue. In addition, ITT analysis tends to bias the results towards no difference, and therefore the effect may be smaller than in reality.

### **3.3.3 Appraising the quality of evidence by outcomes**

The evidence for outcomes from the included RCTs and observational studies (when appropriate) was evaluated and presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>). The software (GRADEpro) developed by the GRADE working group was used to assess the evidence quality for each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of two adjacent sections: the "Clinical/Economic Study Characteristics" table includes details of the quality assessment while the "Clinical /Economic Summary of Findings" table

includes pooled outcome data and an absolute measure of the intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 2. The main criteria considered in the rating of these elements are discussed below (see section 3.3.4). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

**Table 1: Description of quality elements in GRADE for intervention studies**

Quality element	Description
Risk of bias ('Study Limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

**Table 2: Levels of quality elements in GRADE**

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

**Table 3: Overall quality of outcome evidence in GRADE**

Level	Description
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect
Moderate ⊕⊕⊕○	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low ⊕⊕○○	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low ⊕○○○	Any estimate of effect is very uncertain

### 3.3.4 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW.
2. The rating was then downgraded for the specified criteria: Risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (that had not previously been downgraded) was upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated at 1 or 2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in the following sections (3.3.5 to 3.3.8).

### 3.3.5 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error (for example, if a study were carried out several times there would be a consistently wrong answer, and the results would be inaccurate).

The risk of bias for a given study and outcome is associated with the risk of over or underestimation of true effect.

The risks of bias are listed in Table 4.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

**Table 4: Risk of bias in randomised trials**

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomised trials with allocation by day of week, birth date, chart number, etc.)
Lack of blinding	Patients, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: <ul style="list-style-type: none"> <li>• Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules</li> <li>• Use of unvalidated patient-reported outcomes</li> </ul>

Risk of bias	Explanation
	<ul style="list-style-type: none"> <li>Recruitment bias in cluster randomised trials</li> </ul>

Risk of bias (randomization method, blinding and allocation concealment, loss to follow up) and overall quality of included studies in the NMA was summarized and taken into account in the interpretation of results.

For prognostic studies, quality was assessed using the checklist for Prognostic studies (NICE Guidelines Manual, 2009<sup>151</sup>). The quality rating was derived by assessing the risk of bias across 6 domains; selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed per outcome. A summary table on the quality of prognostic studies is presented at the beginning of each review to summarize the risk of bias across the 5 domains.

More details about the quality assessment for prognostic studies are shown below:

1. The study sample represents the population of interest with regard to key characteristics – ulcerative colitis population, source of sample and inclusion/ exclusion criteria adequately described,
2. Loss to follow up is unrelated to key characteristics, sufficient to limit potential bias – reasons for loss to follow up adequately described.
3. The prognostic factor of interest is adequately measured in study participants.
4. The outcome of interest is adequately measured in study participants.
5. Important potential confounders are appropriately accounted for and the ratio of events/covariate is acceptable (rule of thumb is more than ten).
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of valid results; multivariable analysis is preferred.

### 3.3.6 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in the underlying treatment effect.

Heterogeneity in a meta-analysis was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C). Subgroup analysis is reported after the GRADE evidence profile in which heterogeneity is reported.

When heterogeneity existed (Chi square  $p < 0.1$  or I-squared inconsistency statistic of  $> 50\%$  or evidence from examining forest plots), but no plausible explanation could be found the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty in the evidence contributed by the inconsistency in the results. In addition to the I-square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes.

### 3.3.7 Indirectness

Directness relates to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size.

### 3.3.8 Imprecision

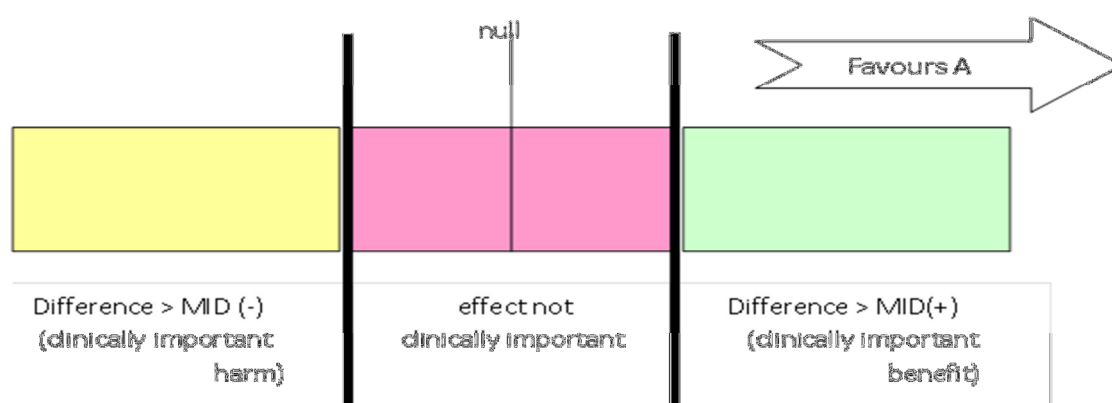
Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that we don't know whether there is a clinically important difference between

interventions. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead we are concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the confidence interval and the more certain we are in the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the confidence interval of the effect estimate is relevant to decision making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision making zones can be identified, bounded by the thresholds for clinical importance (MID) for benefit and for harm (the MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B and this difference is clinically important to patients (favours B)).

**Figure 2: Imprecision illustration**



- When the confidence interval of the effect estimate is wholly contained in one of the three zones (e.g. clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit or the effect is not clinically important or there is a clinically important harm), so there is no imprecision.
- When a wide confidence interval lies partly in each of two zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone); the confidence interval is consistent with two decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by one ("serious imprecision").
- If the confidence interval of the effect estimate crosses into three zones, this is considered to be very imprecise evidence because the confidence interval is consistent with three clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by two in the GRADE analysis ("very serious imprecision").
- Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the two confidence limits.
- The literature was searched for established MIDs for the selected outcomes in the evidence reviews, but no results were found. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community of ulcerative colitis but they confirmed the absence of research in the area. Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to a RR clinically important threshold of 0.75 or 1.25 respectively.



This default MID was used for all the outcomes in the interventions evidence reviews.

### **Publication bias**

Downgrading for publication bias would only be carried out if the GDG were aware that there was serious publication bias for that particular outcome. Such downgrading was not carried out for this guideline.

### **Assessing clinical importance**

The GDG assessed the evidence by outcome in order to determine if there was, or was potentially, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, the relative effect of estimates for binary outcomes were converted into absolute effects using GRADEpro software: the median control group risk across studies was used to calculate the absolute effect and its 95% confidence interval from the pooled risk ratio.

The assessment of benefit/harm/no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardized across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10% cut off) achieved the outcome of interest (if positive) in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative. The cut off point for adverse events was lower and considered for each individual adverse and serious adverse event outcome. This assessment was carried out by the GDG for each outcome. The GDG used the assessment of clinical importance for the outcomes alongside the evidence quality and the uncertainty in the effect estimates to make an overall judgement on the balance of benefit and harms of an intervention.

### **Evidence statements**

Evidence statements are summary statements that are presented after the GRADE profiles, summarizing the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty/uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between two tested treatments).
- A description of the overall quality of evidence (GRADE overall quality).

## **3.4 Evidence of cost-effectiveness**

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

### **3.4.1 Literature review**

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.

- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual<sup>151</sup>.
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

#### 3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix F<sup>151</sup>) and the health economics research protocol in Appendix C.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were considered by the GDG to inform the possible economic implication of the recommendation they wished to make.

#### 3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix H<sup>151</sup>. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.<sup>161</sup>

**Table 5: Content of NICE economic profile**

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*:

Item	Description
	<ul style="list-style-type: none"> <li>• Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost-effectiveness.</li> <li>• Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost-effectiveness.</li> </ul> <p>Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost-effectiveness.</p>
Limitations	<p>An assessment of methodological quality of the study*:</p> <ul style="list-style-type: none"> <li>• Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness.</li> <li>• Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness</li> <li>• Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.</li> </ul>
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost-effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Limitations and applicability were assessed using the economic evaluation checklist from *The Guidelines Manual*, Appendix H<sup>151</sup>

### 3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the health economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See AppendixL for details of the health economic analysis/analyses undertaken for the guideline.

### 3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money<sup>150,151</sup>.

In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'<sup>150</sup>.

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

### 3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix G.
- Summary of clinical (GRADE tables) and economic evidence and quality (as presented in chapters 5-9).
- Forest plots and ROC curves (Appendix H).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix L).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the trade off between benefits, harms and costs of different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm was considered (clinical effectiveness), using the critical outcomes. When this was done informally, the GDG took into account the clinical benefits/harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified the costs. Results of the NMAs was also taken into account in the drafting of recommendations and were incorporated in the health economic modelling for considering the most clinical and cost-effective treatment.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations included the balance between potential harms and benefits, economic or other implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG could also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation. The wording of recommendations was agreed by the GDG and focused on the following factors:

- on the actions health professionals need to take

- include what readers need to know
- reflect the strength of the recommendation (for example the word “offer” was used for strong recommendations and “consider” for weak recommendations)
- emphasise the involvement of the patient (and/or their carers if needed) in decisions on treatment and care
- follow NICE’s standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the ‘Recommendations and link to evidence’ sections within each chapter.

### **3.5.1 Research recommendations**

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

### **3.5.2 Validation process**

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

### **3.5.3 Updating the guideline**

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

### **3.5.4 Disclaimer**

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

### **3.5.5 Funding**

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

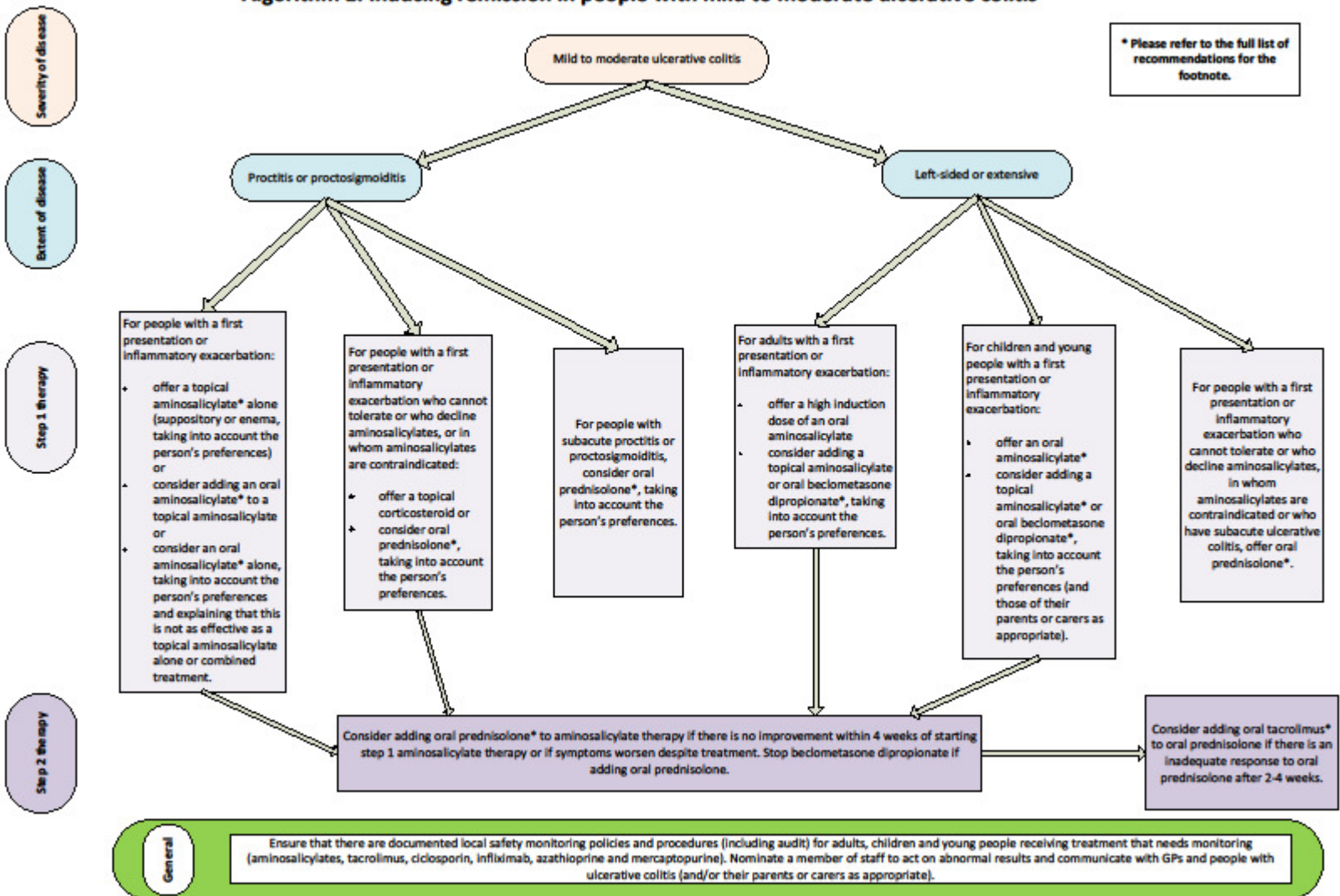
## 4 Guideline summary

### 4.1 Algorithms

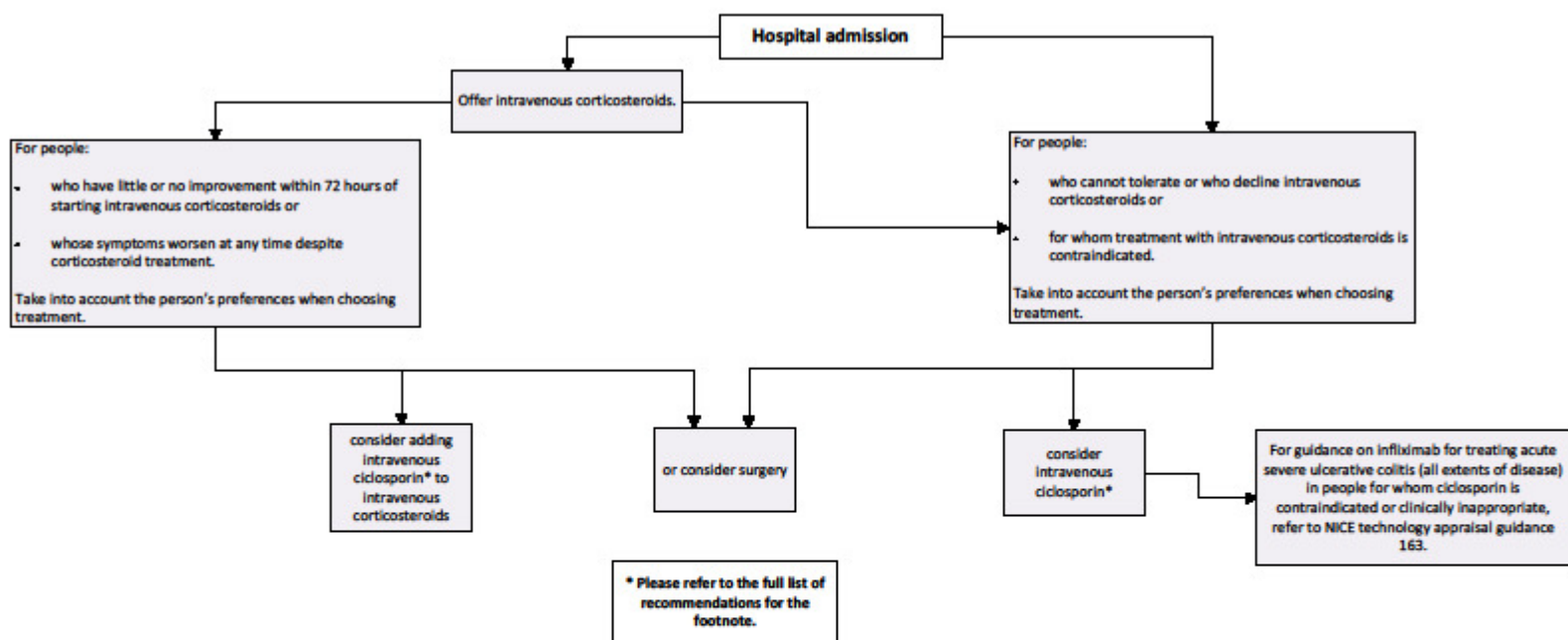
Please see the next two pages for the following two algorithms:

- Algorithm 1: Inducing remission in people with mild to moderate ulcerative colitis.
- Algorithm 2: Inducing remission in people with acute severe ulcerative colitis (all extents of disease).

**Algorithm 1: Inducing remission in people with mild to moderate ulcerative colitis**



## Algorithm 2: Inducing remission in people with acute severe ulcerative colitis (all extents of disease)



### General

Assess and document on admission, and then daily, the likelihood that the person will need surgery.

Be aware that there may be an increased likelihood of needing surgery for people with any of the following:

- stool frequency more than 8 per day
- pyrexia
- tachycardia
- an abdominal X-ray showing colonic dilatation
- low albumin, low haemoglobin, high platelet count or C-reactive protein (CRP) above 45 mg/litre (bear in mind that normal values may be different in pregnant women).

Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring (aminosalicylates, tacrolimus, ciclosporin, infliximab, azathioprine and mercaptopurine). Nominate a member of staff to act on abnormal results and communicate with GPs and people with ulcerative colitis (and/or their parents or carers as appropriate).

- Ensure that a gastroenterologist and a colorectal surgeon collaborate to provide treatment and management.
- Ensure that the composition of the multidisciplinary team is appropriate for the age of the person.
- Seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person.
- Ensure that the obstetric and gynaecology team is included when treating a pregnant woman.



## 4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected 10 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual.<sup>151</sup> The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

### Patient information and support

- Discuss the disease and associated symptoms, treatment options and monitoring:
    - o with the person with ulcerative colitis, and their family members or carers as appropriate **and**
    - o within the multidisciplinary team (the composition of which should be appropriate for the age of the person) at every opportunity.
- Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138).

### Inducing remission: step 1 therapy for mild to moderate ulcerative colitis

- To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis:
  - o offer a topical aminosalicylate<sup>a</sup> alone (suppository or enema, taking into account the person's preferences) **or**
  - o consider adding an oral aminosalicylate<sup>b</sup> to a topical aminosalicylate **or**
  - o consider an oral aminosalicylate<sup>b</sup> alone, taking into account the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment.
- To induce remission in adults with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:
  - o offer a high induction dose of an oral aminosalicylate
  - o consider adding a topical aminosalicylate or oral beclometasone dipropionate<sup>c</sup>, taking into account the person's preferences.
- To induce remission in children and young people with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:
  - o offer an oral aminosalicylate<sup>d</sup>

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<sup>a</sup> At the time of publication (June 2013), 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.

<sup>b</sup> At the time of publication (June 2013), 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.

<sup>c</sup> At the time of publication (June 2013), 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'. 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.

<sup>d</sup> At the time of publication (June 2013), 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. Dosing requirements for children should be calculated by body weight, as described in the BNF.

- o consider adding a topical aminosalicylate<sup>a</sup> or oral beclometasone dipropionate<sup>e</sup>, taking into account the person's preferences (and those of their parents or carers as appropriate).

### **Inducing remission: step 2 therapy for acute severe ulcerative colitis**

- Consider adding intravenous ciclosporin<sup>f</sup> to intravenous corticosteroids or consider surgery for people:
  - o who have little or no improvement within 72 hours of starting intravenous corticosteroids **or**
  - o whose symptoms worsen at any time despite corticosteroid treatment.

Take into account the person's preferences when choosing treatment.

### **Monitoring treatment**

- Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring (aminosalicylates, tacrolimus, ciclosporin, infliximab, azathioprine and mercaptopurine). Nominate a member of staff to act on abnormal results and communicate with GPs and people with ulcerative colitis (and/or their parents or carers as appropriate).

### **Assessing likelihood of needing surgery**

- Assess and document on admission, and then daily, the likelihood of needing surgery for people admitted to hospital with acute severe ulcerative colitis.

### **Information about treatment options for people who are considering surgery**

- For people with ulcerative colitis who are considering surgery, ensure that a specialist (such as a gastroenterologist or a nurse specialist) gives the person (and their family members or carers as appropriate) information about all available treatment options, and discusses this with them. Information should include the benefits and risks of the different treatments and the potential consequences of no treatment.
- After surgery, ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives the person (and their family members or carers as appropriate) information about managing the effects on bowel function. This should be specific to the type of surgery performed (ileostomy or ileoanal pouch) and could include the following:
  - o strategies to deal with the impact on their physical, psychological and social wellbeing
  - o where to go for help if symptoms occur
  - o sources of support and advice.

### **Maintaining remission**

- Consider a once-daily dosing regimen for oral aminosalicylates<sup>g</sup> when used for maintaining remission. Take into account the person's preferences, and explain that once-daily dosing can be more effective, but may result in more side effects.

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<sup>e</sup> At the time of publication (June 2013), beclometasone dipropionate 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.

<sup>f</sup> At the time of publication (June 2013), ciclosporin did not have a UK marketing authorisation for this indication. 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.

<sup>g</sup> At the time of publication (June 2013), not all oral aminosalicylates had a UK marketing authorisation for once-daily dosing. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed

## 4.3 Full list of recommendations

### Adults, children and young people

This guideline covers people of all ages with a diagnosis of ulcerative colitis. All recommendations relate to adults, children and young people unless specified otherwise. These terms are defined as follows:

- adults: 18 years or older
- children: 11 years or younger
- young people: 12 to 17 years.

### Severity of ulcerative colitis

#### Mild, moderate and severe

In this guideline, the categories of mild, moderate and severe are used to describe ulcerative colitis:

- In adults these categories are based on the Truelove and Witts' severity index (see Table 6). This table is adapted from the Truelove and Witts' criteria.<sup>216</sup>
- In children and young people these categories are based on the Paediatric Ulcerative Colitis Activity Index (PUCAI) (see Table 7).<sup>218</sup>

**Table 6: Truelove and Witts' severity index**

	Mild	Moderate	Severe
<b>Bowel movements (no. per day)</b>	Fewer than 4	4–6	6 or more plus at least one of the features of systemic upset, (marked with * below)
<b>Blood in stools</b>	No more than small amounts of blood	Between mild and severe	Visible blood
<b>Pyrexia (temperature greater than 37.8°C) *</b>	No	No	Yes
<b>Pulse rate greater than 90 bpm *</b>	No	No	Yes
<b>Anaemia *</b>	No	No	Yes
<b>Erythrocyte sedimentation rate (mm/hr) *</b>	30 or below	30 or below	Above 30

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**Table 7: Paediatric Ulcerative Colitis Activity Index (PUCAI)**

Disease severity is defined by the following scores:

- severe: 65 or above

consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

- moderate: 35-64
- mild: 10-34
- remission (disease not active): below 10.

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal stools (any episode causing waking)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI (0-85)	

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### Subacute

The term 'subacute' is also used in this guideline to describe ulcerative colitis, but this is not covered by the Truelove and Witts' severity index or the PUCAI. The following definition (based on that in NICE technology appraisal guidance 140) is used: subacute ulcerative colitis is defined as moderately

to severely active ulcerative colitis that would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of urgent surgical intervention.

### Patient information and support

1. Discuss the disease and associated symptoms, treatment options and monitoring:
  - with the person with ulcerative colitis, and their family members or carers as appropriate **and**
  - within the multidisciplinary team (the composition of which should be appropriate for the age of the person) at every opportunity.

Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138).

2. Discuss the possible nature, frequency and severity of side effects of drug treatment for ulcerative colitis with the person, and their family members or carers as appropriate. Refer to Medicines adherence (NICE clinical guideline 76).
3. Give the person, and their family members or carers as appropriate, information about their risk of developing colorectal cancer and about colonoscopic surveillance, in line with the NICE clinical guidelines on:
  - Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE clinical guideline 118)
  - Referral for suspected cancer (NICE clinical guideline 27)<sup>h</sup>.

### Inducing remission in people with ulcerative colitis

#### Treating mild to moderate ulcerative colitis: step 1 therapy

##### *Proctitis and proctosigmoiditis*

4. To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis:
  - offer a topical aminosalicylate<sup>i</sup> alone (suppository or enema, taking into account the person's preferences) **or**
  - consider adding an oral aminosalicylate<sup>j</sup> to a topical aminosalicylate **or**
  - consider an oral aminosalicylate<sup>j</sup> alone, taking into account the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment.
5. To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis who cannot tolerate or who decline aminosalicylates, or in whom aminosalicylates are contraindicated:
  - offer a topical corticosteroid **or**
  - consider oral prednisolone<sup>k</sup>, taking into account the person's preferences.

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<sup>h</sup> This guideline is being updated (publication date to be confirmed).

<sup>i</sup> At the time of publication (June 2013), 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.

<sup>j</sup> At the time of publication (June 2013), 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.

<sup>k</sup> Refer to the BNF for guidance on stopping oral prednisolone therapy.

6. To induce remission in people with subacute proctitis or proctosigmoiditis, consider oral prednisolone<sup>k</sup>, taking into account the person's preferences.

***Left-sided and extensive ulcerative colitis***

7. To induce remission in adults with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:
  - offer a high induction dose of an oral aminosalicylate
  - consider adding a topical aminosalicylate or oral beclometasone dipropionate<sup>l</sup>, taking into account the person's preferences.
8. To induce remission in children and young people with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:
  - offer an oral aminosalicylate<sup>m</sup>
  - consider adding a topical aminosalicylate<sup>n</sup> or oral beclometasone dipropionate<sup>o</sup>, taking into account the person's preferences (and those of their parents or carers as appropriate).
9. To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis who cannot tolerate or who decline aminosalicylates, in whom aminosalicylates are contraindicated or who have subacute ulcerative colitis, offer oral prednisolone<sup>k</sup>.

**Treating mild to moderate ulcerative colitis: step 2 therapy**

***All extents of disease***

10. Consider adding oral prednisolone<sup>k</sup> to aminosalicylate therapy to induce remission in people with mild to moderate ulcerative colitis if there is no improvement within 4 weeks of starting step 1 aminosalicylate therapy or if symptoms worsen despite treatment. Stop beclometasone dipropionate if adding oral prednisolone.
11. Consider adding oral tacrolimus<sup>p</sup> to oral prednisolone to induce remission in people with mild to moderate ulcerative colitis if there is an inadequate response to oral prednisolone after 2–4 weeks.

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<sup>l</sup> At the time of publication (June 2013), 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'. 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.

<sup>m</sup> At the time of publication (June 2013), 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. Dosing requirements for children should be calculated by body weight, as described in the BNF.

<sup>n</sup> At the time of publication (June 2013), 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.

<sup>o</sup> At the time of publication (June 2013), beclometasone dipropionate 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.

<sup>p</sup> At the time of publication (June 2013), tacrolimus did not have a UK marketing authorisation for this indication. 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.

12. For guidance on infliximab for treating subacute ulcerative colitis (all extents of disease), refer to *Infliximab for subacute manifestations of ulcerative colitis* (NICE technology appraisal guidance 140).

### **Treating acute severe ulcerative colitis: all extents of disease**

#### ***The multidisciplinary team***

13. For people admitted to hospital with acute severe ulcerative colitis:

- ensure that a gastroenterologist and a colorectal surgeon collaborate to provide treatment and management
- ensure that the composition of the multidisciplinary team is appropriate for the age of the person
- seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person
- ensure that the obstetric and gynaecology team is included when treating a pregnant women.

#### **Step 1 therapy**

14. For people admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation):

- offer intravenous corticosteroids to induce remission **and**
- assess the likelihood that the person will need surgery (see recommendation 19).

15. Consider intravenous ciclosporin<sup>q</sup> or surgery for people:

- who cannot tolerate or who decline intravenous corticosteroids **or**
- for whom treatment with intravenous corticosteroids is contraindicated.

Take into account the person's preferences when choosing treatment.

#### **Step 2 therapy**

16. Consider adding intravenous ciclosporin<sup>q</sup> to intravenous corticosteroids or consider surgery for people:

- who have little or no improvement within 72 hours of starting intravenous corticosteroids **or**
- whose symptoms worsen at any time despite corticosteroid treatment.

Take into account the person's preferences when choosing treatment.

17. For guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to *Infliximab for acute exacerbations of ulcerative colitis* (NICE technology appraisal guidance 163).

### **Monitoring treatment**

18. Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring (aminosalicylates, tacrolimus, ciclosporin, infliximab, azathioprine and mercaptopurine).

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<sup>q</sup> At the time of publication (June 2013), ciclosporin did not have a UK marketing authorisation for this indication. 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.

Nominate a member of staff to act on abnormal results and communicate with GPs and people with ulcerative colitis (and/or their parents or carers as appropriate).

#### **Assessing likelihood of needing surgery**

19. Assess and document on admission, and then daily, the likelihood of needing surgery for people admitted to hospital with acute severe ulcerative colitis.
20. Be aware that there may be an increased likelihood of needing surgery for people with any of the following:
  - stool frequency more than 8 per day
  - pyrexia
  - tachycardia
  - an abdominal X-ray showing colonic dilatation
  - low albumin, low haemoglobin, high platelet count or C-reactive protein (CRP) above 45 mg/litre (bear in mind that normal values may be different in pregnant women).

#### **Information about treatment options for people who are considering surgery**

These recommendations apply to anyone with ulcerative colitis considering elective surgery. The principles can also be applied to people requiring emergency surgery.

#### **Information when considering surgery**

21. For people with ulcerative colitis who are considering surgery, ensure that a specialist (such as a gastroenterologist or a nurse specialist) gives the person (and their family members or carers as appropriate) information about all available treatment options, and discusses this with them. Information should include the benefits and risks of the different treatments and the potential consequences of no treatment.
22. Ensure that the person (and their family members or carers as appropriate) has sufficient time and opportunities to think about the options and the implications of the different treatments.
23. Ensure that a colorectal surgeon gives any person who is considering surgery (and their family members or carers as appropriate) specific information about what they can expect in the short and long term after surgery, and discusses this with them.
24. Ensure that a specialist (such as a colorectal surgeon, a gastroenterologist, an inflammatory bowel disease nurse specialist or a stoma nurse) gives any person who is considering surgery (and their family members or carers as appropriate) information about:
  - diet
  - sensitive topics such as sexual function
  - effects on lifestyle
  - psychological wellbeing
  - the type of surgery, the possibility of needing a stoma and stoma care.
25. Ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives any person who is having surgery (and their family members or carers as appropriate) specific information about the siting, care and management of stomas.

#### **Information after surgery**

26. After surgery, ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives the person (and their family members or carers as appropriate) information about managing the effects on bowel function. This should be



specific to the type of surgery performed (ileostomy or ileoanal pouch) and could include the following:

- strategies to deal with the impact on their physical, psychological and social wellbeing
- where to go for help if symptoms occur
- sources of support and advice.

## **Maintaining remission in people with ulcerative colitis**

### ***Proctitis and proctosigmoiditis***

27. To maintain remission after a mild to moderate inflammatory exacerbation of proctitis or proctosigmoiditis, consider the following options, taking into account the person's preferences:

- a topical aminosalicylate<sup>r</sup> alone (daily or intermittent) **or**
- an oral aminosalicylate<sup>s</sup> plus a topical aminosalicylate<sup>r</sup> (daily or intermittent) **or**
- an oral aminosalicylate<sup>s</sup> alone, explaining that this may not be as effective as combined treatment or an intermittent topical aminosalicylate alone.

### ***Left-sided and extensive ulcerative colitis***

28. To maintain remission in adults after a mild to moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis:

- offer a low maintenance dose of an oral aminosalicylate
- when deciding which oral aminosalicylate to use, take into account the person's preferences, side effects and cost.

29. To maintain remission in children and young people after a mild to moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis:

- offer an oral aminosalicylate<sup>t</sup>
- when deciding which oral aminosalicylate to use, take into account the person's preferences (and those of their parents or carers as appropriate), side effects and cost.

### ***All extents of disease***

30. Consider oral azathioprine<sup>u</sup> or oral mercaptopurine<sup>u</sup> to maintain remission:

- after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids **or**
- if remission is not maintained by aminosalicylates.

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<sup>r</sup> At the time of publication (June 2013), 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.

<sup>s</sup> At the time of publication (June 2013), 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.

<sup>t</sup> At the time of publication (June 2013), 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. Dosing requirements for children should be calculated by body weight, as described in the BNF.

<sup>u</sup> Although use is common in UK clinical practice, at the time of publication (June 2013) azathioprine and mercaptopurine did not have a UK marketing authorisation for this indication. 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.

31. To maintain remission after a single episode of acute severe ulcerative colitis:

- consider oral azathioprine<sup>u</sup> or oral mercaptopurine<sup>u</sup>
- consider oral aminosalicylates in people who cannot tolerate or who decline azathioprine and/or mercaptopurine, or in whom azathioprine and/or mercaptopurine are contraindicated.

### **Dosing regimen for oral aminosalicylates**

32. Consider a once-daily dosing regimen for oral aminosalicylates<sup>v</sup> when used for maintaining remission. Take into account the person's preferences, and explain that once-daily dosing can be more effective, but may result in more side effects.

### **Pregnant women**

33. When caring for a pregnant woman with ulcerative colitis:

- Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gynaecology, and gastroenterology).
- Give her information about the potential risks and benefits of medical treatment to induce or maintain remission and of no treatment, and discuss this with her. Include information relevant to a potential admission for an acute severe inflammatory exacerbation.

### **Monitoring**

#### **Monitoring bone health**

##### **Adults**

34. For recommendations on assessing the risk of fragility fracture in adults, refer to Osteoporosis: assessing the risk of fragility fracture (NICE clinical guideline 146).

##### **Children and young people**

35. Consider monitoring bone health in children and young people with ulcerative colitis in the following circumstances:

- during chronic active disease
- after treatment with systemic corticosteroids
- after recurrent active disease.

#### **Monitoring growth and pubertal development in children and young people**

36. Monitor the height and body weight of children and young people with ulcerative colitis against expected values on centile charts (and/or z scores) at the following intervals according to disease activity:

- every 3–6 months:
  - o if they have an inflammatory exacerbation and are approaching or undergoing puberty **or**
  - o if there is chronic active disease **or**
  - o if they are being treated with systemic corticosteroids
- every 6 months during pubertal growth if the disease is inactive
- every 12 months if none of the criteria above are met.

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<sup>v</sup> At the time of publication (June 2013), not all oral aminosalicylates had a UK marketing authorisation for once-daily dosing. 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.

37. Monitor pubertal development in young people with ulcerative colitis using the principles of Tanner staging, by asking screening questions and/or carrying out a formal examination.
38. Consider referral to a secondary care paediatrician for pubertal assessment and investigation of the underlying cause if a young person with ulcerative colitis:
  - has slow pubertal progress **or**
  - has not developed pubertal features appropriate for their age.
39. Monitoring of growth and pubertal development:
  - can be done in a range of locations (for example, at routine appointments, acute admissions or urgent appointments in primary care, community services or secondary care)
  - should be carried out by appropriately trained healthcare professionals as part of the overall clinical assessment (including disease activity) to help inform the need for timely investigation, referral and/or interventions, particularly during pubertal growth.

If the young person prefers self-assessment for monitoring pubertal development, this should be facilitated where possible and they should be instructed on how to do this.
40. Ensure that relevant information about monitoring of growth and pubertal development and about disease activity is shared across services (for example, community, primary, secondary and specialist services). Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138) in relation to continuity of care.

## 4.4 Key research recommendations

1. What is the clinical and cost effectiveness of prednisolone compared with aminosalicylates for the induction of remission for people with moderate ulcerative colitis?
2. What is the clinical and cost effectiveness of prednisolone plus an aminosalicylate compared with beclometasone plus an aminosalicylate for induction of remission for people with moderate ulcerative colitis?
3. What are the benefits, risks and cost effectiveness of methotrexate, ciclosporin, tacrolimus, adalimumab and infliximab compared with each other and with placebo for induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids?
4. What is the clinical and cost effectiveness of regular maintenance treatment compared with no regular treatment (but rapid standard treatment if a relapse occurs) in specific populations with mild to moderate ulcerative colitis?
5. To develop and validate a risk tool that predicts the likelihood of needing surgery for adults admitted to hospital with acute severe ulcerative colitis.

## 5 Inducing remission in people with ulcerative colitis

### Adults, children and young people

This guideline covers people of all ages with a diagnosis of ulcerative colitis. All recommendations relate to adults, children and young people unless specified otherwise. These terms are defined as follows:

- adults: 18 years or older
- children: 11 years or younger
- young people: 12 to 17 years.

### Severity of ulcerative colitis

#### Mild, moderate and severe

In this guideline, the categories of mild, moderate and severe are used to describe ulcerative colitis:

- In adults these categories are based on the Truelove and Witts' severity index (see Table 8). This table is adapted from the Truelove and Witts' criteria.<sup>216</sup>
- In children and young people these categories are based on the Paediatric Ulcerative Colitis Activity Index (PUCAI) (see Table 9).<sup>218</sup>

**Table 8: Truelove and Witts' severity index**

	Mild	Moderate	Severe
<b>Bowel movements (no. per day)</b>	Fewer than 4	4–6	6 or more plus at least one of the features of systemic upset, (marked with * below)
<b>Blood in stools</b>	No more than small amounts of blood	Between mild and severe	Visible blood
<b>Pyrexia (temperature greater than 37.8°C) *</b>	No	No	Yes
<b>Pulse rate greater than 90 bpm *</b>	No	No	Yes
<b>Anaemia *</b>	No	No	Yes
<b>Erythrocyte sedimentation rate (mm/hr) *</b>	30 or below	30 or below	Above 30

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**Table 9: Paediatric Ulcerative Colitis Activity Index (PUCAI)**

Disease severity is defined by the following scores:

- severe: 65 or above

- moderate: 35–64
- mild: 10–34
- remission (disease not active): below 10.

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal stools (any episode causing waking)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI (0-85)	

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### Subacute

The term 'subacute' is also used in this guideline to describe ulcerative colitis, but this is not covered by the Truelove and Witts' severity index or the PUCAI. The following definition (based on that in NICE technology appraisal guidance 140) is used: subacute ulcerative colitis is defined as moderately

to severely active ulcerative colitis that would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of urgent surgical intervention.

## 5.1 Clinical introduction: Pharmacological treatment

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 call to defaecation and abdominal pain.

The extent of colon and rectum affected by inflammation may vary. Inflammation affecting the rectum alone may be referred to as proctitis; proctosigmoiditis if the rectum and sigmoid colon are affected; left-sided colitis if the inflammation extends proximally from the rectum to no further than the splenic flexure; sub-total colitis if the inflammation extends beyond the splenic flexure, but does not affect the whole colon; total colitis, or pan-colitis, if the entire colon is affected. Extensive colitis refers to colitis that is greater than left-sided.

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.

There are a number of drug factors to consider when choosing treatment. These include:

- choice of drug
- site and mechanism of drug release – for orally administered 5-aminosalicylic acid preparations
- route of administration – which may include combinations of different routes (eg oral and rectal administration)
- dose.

There are also patient-related factors which may influence the choice of treatment for induction of remission, which would include:

- clinical severity of the exacerbation
- extent of inflammation
- patient preference
- dosing regimens, for example, those which may enhance adherence to treatment.

The most widely used drugs in this situation are corticosteroids and aminosalicylate preparations of which 5-aminosalicylic acid is the active moiety. Depending on the preparation, 5-aminosalicylic acid is released through differing mechanisms including loss of integrity of an outer coating or cleavage of a diazo bond from a pro-drug. The aim of this release, in people with ulcerative colitis, is to deliver adequate levels of 5-aminosalicylic acid to the colon and rectum. Systemically bioavailable corticosteroids, such as prednisolone, have been widely used, but concern remains about their side-effects. Orally administered beclometasone has topical mucosal activity, but is extensively metabolised with less systemic bioavailability. Immunomodulator drugs (azathioprine, mercaptopurine, ciclosporin, tacrolimus and methotrexate) are also used.

There is considerable variation and debate about appropriate outcome measures in studies examining induction of remission. A wide range of different definitions and end-points were used in studies, and in order to ensure that important studies were not excluded from the review, the GDG

agreed, a priori, to use authors' definitions of remission. Many studies also include clinical improvement and not remission as an end-point, and it was felt important, particularly by patient members of the GDG, that this was included as a critical outcome for consideration by the GDG.

Acute severe ulcerative colitis is regarded as a medical emergency and requires hospital admission for intravenous corticosteroids and prophylaxis against venous thromboembolism. Careful monitoring is then required to ensure that an adequate response occurs or that there is timely, further intervention, such as ciclosporin, anti-TNF agents or the consideration of emergency surgery. The use of anti-TNF agents is covered by 'Infliximab for the treatment of acute exacerbations of ulcerative colitis' NICE technology appraisal guidance 163. Evidence relating to the use of systemic corticosteroids and ciclosporin was reviewed in this chapter. Parameters that would help in assessing response, and in selecting patients at higher risk of colectomy (and therefore who may benefit from escalation of medical therapy), are examined in detail in section 5.48.

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

For full details see review protocol in Appendix C.

A matrix showing where evidence was identified is given in Table 10. A cross in the box indicates evidence was found and the evidence has been reviewed in this chapter an empty box indicates no evidence was found.

**Table 10: Induction of remission matrix of comparisons**

Topical corticosteroids	Prednisolone																			
	Hydrocortisone																			
	Budesonide	X	X	X																
Topical aminosalicylates	Mesalazine*	X	X	X	X															
	Sulphasalazine																			
Oral corticosteroids	Prednisolone																			
	Budesonide																			
	Beclometasone																			
Oral aminosalicylates	Mesalazine*				X			X	X	X										
	Olsalazine										X									
	Balsalazide										X									
	Sulphasalazine						X					X								
Combination treatment	Mesalazine & beclometasone										X									
	Oral & topical mesalazine										X							X		
Immunomodulators	Methotrexate																			
	Azathioprine																			
	Mercaptopurine																			
	Tacrolimus																			X
	Placebo			X	X						X	X	X	X			X	X		X
		Prednisolone	Hydrocortisone	Budesonide	Mesalazine*	Sulphasalazine	Prednisolone	Budesonide	Beclometasone dipropionate	Mesalazine *	Olsalazine	Balsalazide	Sulphasalazine	Mesalazine & beclometasone	Oral & topical mesalazine	Methotrexate	Azathioprine	Mercaptopurine	Tacrolimus	
		Topical corticosteroids			Topical aminosalicylates		Oral corticosteroids			Oral aminosalicylates				Combinations		Immunomodulators				

Note: \* ASA or 5-ASA that were not named in the trials have been included under this drug category.



The reviews for the induction of remission in people with mild to moderate ulcerative colitis are presented in the following order:

- Topical aminosaliclates (section 5.3)
- Topical corticosteroids (section 5.7)
- Topical aminosaliclates versus topical corticosteroids (section 5.11)
- Oral aminosaliclates (section 5.15)
- Oral corticosteroids (section 5.19)
- Oral aminosaliclates versus oral corticosteroids (section 5.23)
- Topical aminosaliclates versus oral aminosaliclates (section 5.27)
- Topical corticosteroids versus oral corticosteroids (section 5.31)
- Immunomodulators (section 5.36).

For all the reviews in this chapter an author defined definition of the clinical, endoscopic, clinical and endoscopic remission and clinical improvement was used. There are an extensive number of different indices used in the published literature and many of these indices are not validated. Including all studies that have author defined definitions and limiting the review to studies that use one index carries a high risk of bias however, by choosing one index the GDG felt that too many studies would be excluded and there would be a lack of evidence to consider. The bias associated with using the author's definitions was taken into account when analysing the data.

There were no setting restrictions. 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 more likely to be maintenance of remission treatment.

The following subgroups were considered for subgroup analysis in the event of heterogeneity in the meta-analysis:

- Disease severity: mild to moderate
- Dose
- Disease extent: proctitis, proctosigmoiditis, left-sided ulcerative colitis, extensive ulcerative colitis
- Age (adults, children and young people)
- Formulation (foam, enema, suppository, tablet, capsule).

### 5.3 Clinical evidence: Topical aminosaliclates

Eighteen studies were included in the review.<sup>4-6,18,29-34,43,84,117,118,165,168,226,227</sup> Evidence from these are summarised in the clinical GRADE evidence profiles below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

The reviews in this section are topical aminosaliclates versus placebo (section 5.4.1) and topical aminosaliclates versus topical aminosaliclates (preparation comparison (section 5.4.2), dose comparison (section 5.4.3), regimen comparison (section 5.4.4) and regimen and dose comparison (section 5.4.5)).

"Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis" was published by the Cochrane collaboration in 2003 and updated in 2010<sup>137</sup>. The review included 38 studies which compared the following:

- Rectal ASA versus placebo
- Rectal ASA versus rectal steroids
- Rectal ASA versus oral ASA

- Rectal ASA versus oral & rectal ASA
- Rectal ASA dose comparison
- Rectal ASA formulation comparison
- Rectal 5-ASA versus rectal 4-ASA
- Frequency of rectal ASA dosing

The Cochrane review concluded that rectal ASA should be considered first line therapy for those patients with mild to moderate active distal ulcerative colitis. No conclusion was made concerning the optimal daily dose and frequency. The Cochrane review was excluded as it only included studies with an extent of disease up to the splenic flexure, excluded child populations (<12years) and it included trials with named preparations that were not available in the UK. These studies included in the Cochrane review were excluded from this review for the following reasons:

- BASILISCO1987; MOLLER1978; PALMER19981: Sulphasalazine is not available in a liquid enema
- BIANCHIPORRO1995: Chronic ulcerative colitis
- GIONCHETTI1999: Gel enemas are not available in the UK
- CAMPIERI1984; ELIALKIM2007; GIONCHETTI1997; GIONCHETTI2005; KAM1996; MALCHOW2002; MULDER1996; SAFDI1997; SUTHERLAND1987: Comparator is not available in the U.K. (Claversal, Rowasa, 4ASA, beclometasone dipropionate enemas)
- MINER2006: Alicaforsen is not included in the scope of the guideline
- SENAGORE1992: Population included idiopathic proctosigmoiditis

## 5.4 Evidence profile

### 5.4.1 Topical aminosalicylates versus placebo

Table 11: Topical aminosalicylates versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical ASA	Placebo	Relative (95% CI)	Absolute		
Clinical remission - 0≤2 weeks												
4	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/199 (37.7%)	9/102 (8.8%)	RR 3.84 (2.05 to 7.19)	251 more per 1000 (from 93 more to 546 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical remission - >2≤4 weeks, random effects												
4	randomised trials	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	none	133/199 (66.8%)	18/102 (17.6%)	RR 4.66 (1.64 to 13.28)	646 more per 1000 (from 113 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical remission - >4≤6 weeks												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	35/54 (64.8%)	23/57 (40.4%)	RR 1.61 (1.11 to 2.33)	246 more per 1000 (from 44 more to 537 more)	⊕⊕OO LOW	CRITICAL
Clinical remission - >6≤8 weeks												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	101/217 (46.5%)	10/70 (14.3%)	RR 3.26 (1.8 to 5.88)	323 more per 1000 (from 114 more to 697 more)	⊕⊕OO LOW	CRITICAL
Clinical remission >2≤4 weeks by extent of disease - Up to the splenic flexure												
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/104 (67.3%)	4/41 (9.8%)	RR 6.71 (2.64 to 17.11)	557 more per 1000 (from 160 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical remission >2≤4 weeks by extent of disease - <20 cm												
2	randomised trials	no serious risk of bias	very serious <sup>6</sup>	no serious indirectness	no serious imprecision	none	63/95 (66.3%)	14/61 (23%)	RR 2.6 (1.65 to 4.07)	367 more per 1000 (from 149 more to 705 more)	⊕⊕OO LOW	CRITICAL
Clinical improvement - 0≤2 weeks, random effects												
5	randomised trials	very serious <sup>1,3</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	none	193/250 (77.2%)	57/155 (36.8%)	RR 2.30 (1.46 to 3.63)	478 more per 1000 (from 169 more to 967 more)	⊕OOO VERY LOW	CRITICAL
Clinical improvement ->2≤4 weeks, random effects												
5	randomised	very	very serious <sup>6</sup>	no serious	no serious	none	201/246	61/145	RR 2.04 (1.28	438 more per 1000	⊕OOO	CRITICAL

	trials	serious <sup>1,3</sup>		indirectness	imprecision		(81.7%)	(42.1%)	to 3.25)	(from 118 more to 947 more)	VERY LOW	
<b>Clinical improvement - &gt;4≤6 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	35/43 (81.4%)	26/37 (70.3%)	RR 1.16 (0.90 to 1.49)	112 more per 1000 (from 70 fewer to 344 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/217 (69.1%)	19/70 (27.1%)	RR 2.55 (1.72 to 3.78)	421 more per 1000 (from 195 more to 755 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement 0≤2 weeks by extent of disease – Up to the splenic flexure</b>												
3	randomised trials	serious <sup>1,3</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	none	121/155 (78.1%)	41/94 (43.6%)	RR 1.84 (1.41 to 2.39)	366 more per 1000 (from 179 more to 606 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement 0≤2 weeks by extent of disease - &lt;20cm</b>												
2	randomised trials	serious <sup>7</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/95 (75.8%)	16/61 (26.2%)	RR 2.77 (1.8 to 4.26)	464 more per 1000 (from 210 more to 855 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Clinical improvement &gt;2≤4 weeks by extent of disease – Up to the splenic flexure</b>												
3	randomised trials	serious <sup>1,3</sup>	very serious <sup>6</sup>	no serious indirectness	no serious imprecision	none	119/151 (78.8%)	38/84 (45.2%)	RR 1.72 (1.3 to 2.26)	326 more per 1000 (from 136 more to 570 more)	⊕OOO VERY LOW	CRITICAL
<b>Clinical improvement &gt;2≤4 weeks by extent of disease - &lt;20cm</b>												
2	randomised trials	serious <sup>7</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/95 (86.3%)	23/61 (37.7%)	RR 2.26 (1.63 to 3.14)	475 more per 1000 (from 238 more to 807 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission - 0≤2 weeks</b>												
3	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/136 (27.9%)	2/71 (2.8%)	RR 7.54 (2.08 to 27.36)	184 more per 1000 (from 30 more to 743 more)	⊕⊕⊕O MODERATE	IMPORTANT
<b>Endoscopic remission - &gt;2≤4 weeks</b>												
4	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	99/199 (49.7%)	11/102 (10.8%)	RR 4.3 (2.46 to 7.5)	356 more per 1000 (from 157 more to 701 more)	⊕⊕⊕O MODERATE	IMPORTANT
<b>Endoscopic remission - &gt;4≤6 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	26/54 (48.1%)	17/57 (29.8%)	RR 1.61 (0.99 to 2.62)	182 more per 1000 (from 3 fewer to 483 more)	⊕⊕OO LOW	IMPORTANT
<b>Endoscopic remission - &gt;6≤8 weeks</b>												

1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/217 (63.1%)	17/70 (24.3%)	RR 2.6 (1.7 to 3.98)	389 more per 1000 (from 170 more to 724 more)	⊕⊕⊕⊕ LOW	IMPORTANT
<b>Clinical and endoscopic remission - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	none	5/14 (35.7%)	0/13 (0%)	RR 10.27 (0.62 to 169.16)	-	⊕⊕⊕⊕ VERY LOW	IMPORTANT
<b>Clinical and endoscopic remission - &gt;4≤6 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/14 (78.6%)	1/13 (7.7%)	RR 10.21 (1.52 to 68.49)	708 more per 1000 (from 40 more to 1000 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
<b>Adverse events</b>												
2	randomised trials	very serious <sup>9</sup>	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	none	1/82 (1.2%)	3/49 (6.1%)	RR 0.29 (0.04 to 2.14)	43 fewer per 1000 (from 59 fewer to 70 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	none	1/54 (1.9%)	4/57 (7%)	RR 0.26 (0.03 to 2.29)	52 fewer per 1000 (from 68 fewer to 91 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
<b>Hospitalisations</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>8</sup>	none	1/54 (1.9%)	4/57 (7%)	RR 0.26 (0.03 to 2.29)	52 fewer per 1000 (from 68 fewer to 91 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment.

<sup>2</sup>  $I^2 > 50\%$  but  $< 75\%$ .

<sup>3</sup> Overall unclear dropout rate.

<sup>4</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>5</sup> Overall unclear method of randomisation and allocation concealment. Unclear drop out rate.

<sup>6</sup>  $I^2 > 75\%$ .

<sup>7</sup> overall unclear allocation concealment.

<sup>8</sup> Crosses both the upper 1.25 and lower 0.75 relative risk (RR) MIDs.

<sup>9</sup> Overall unclear method of randomisation and allocation concealment. No information on extent or severity at baseline.

## Subgroup analysis

A high heterogeneity value was found (73%) for the topical ASA versus placebo comparison: clinical remission at >2≤4 weeks. Sensitivity analysis was carried out on the specified subgroups. None of which were found to explain the heterogeneity. See Table 12 for the study differences. The CAMPIERI1990<sup>29</sup> study has a lower effect compared to the other three studies. This may be due to the CAMPIERI1990 study<sup>29</sup> having a lower risk of bias as the other three studies had an overall unclear method of randomisation and allocation concealment.

**Table 12: Topical aminosaliclates versus placebo: clinical remission at >2≤4 weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
CAMPIERI1990	1-2g	Mild/moderate	<20cm	Suppository	18-75 years
CAMPIERI1990A	1-2g	Mild/moderate	<20cm	Suppository	Range not described
CAMPIERI1991	1-4g	Mild/moderate	Up to the splenic flexure	Liquid enema	>18 years
CAMPIERI1991A	2g	Mild/moderate	Up to the splenic flexure	Liquid enema	>18 years

(a) All the studies had similar mean ages, but not all of them had standard deviations to compare.

High heterogeneity was also found for clinical improvement at 0≤2weeks and >2≤4 weeks (69% and 76% respectively), which included the same four studies in Table 12 and Table 13 plus POKROTNIEKS2000<sup>165</sup>. See Table 13 for the study differences. Sensitivity analysis was carried out on the specified subgroups. Extent of disease did not explain the heterogeneity (see Appendix H). The outlier appears to be the POKROTNIEKS2000 study<sup>165</sup>, but it is unclear as to why the effect is reduced. It may be related to the overall unclear dropout rate.

**Table 13: Topical aminosaliclates versus placebo: clinical improvement 0≤2 weeks & >2≤4weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
CAMPIERI1990	1-2g	Mild/moderate	<20cm	Suppository	18-75 years
CAMPIERI1990A	1-2g	Mild/moderate	<20cm	Suppository	Range not described
CAMPIERI1991	1-4g	Mild/moderate	Up to the splenic flexure	Liquid enema	>18 years
CAMPIERI1991A	2g	Mild/moderate	Up to the splenic flexure	Liquid enema	>18 years
POKROTNIEKS2000	2g	Mild/moderate	Up to left sided colitis	liquid enema	19-69 years

#### 5.4.2 Topical aminosaliclates versus topical aminosaliclates (preparation comparison)

**Table 14: Foam versus liquid enema**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Foam enema	Liquid enema	Relative (95% CI)	Absolute		
Clinical remission - 0≤2 weeks, random effects												
3	randomised trials	serious <sup>1</sup>	serious <sup>2</sup>	no serious indirectness	very serious <sup>3,4</sup>	none	136/312 (43.6%)	113/289 (39.1%)	RR 1.35 (0.80 to 2.27)	137 more per 1000 (from 78 fewer to 497	⊕○○○ VERY LOW	CRITICAL

										more)		
<b>Clinical remission - &gt;2≤4weeks, random effects</b>												
4	randomised trials	very serious <sup>5</sup>	serious <sup>2</sup>	no serious indirectness	no serious imprecision	none	271/409 (66.3%)	269/387 (69.5%)	RR 0.98 (0.81 to 1.17)	14 fewer per 1000 (from 131 fewer to 117 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical improvement - 0≤2 weeks</b>												
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	98/123 (79.7%)	71/110 (64.5%)	RR 1.23 (1.04 to 1.45)	148 more per 1000 (from 26 more to 290 more)	⊕⊕○○ LOW	CRITICAL
<b>Clinical improvement - &gt;2≤4weeks</b>												
3	randomised trials	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	123/147 (83.7%)	110/134 (82.1%)	RR 1.02 (0.91 to 1.13)	16 more per 1000 (from 74 fewer to 107 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Clinical improvement - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>6</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	16/24 (66.7%)	22/24 (91.7%)	RR 0.73 (0.53 to 0.99)	274 fewer per 1000 (from 9 fewer to 431 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission - &gt;2≤4weeks</b>												
4	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	236/409 (57.7%)	246/387 (63.6%)	RR 0.91 (0.81 to 1.01)	57 fewer per 1000 (from 121 fewer to 6 more)	⊕⊕○○ LOW	IMPORTANT
<b>Clinical and endoscopic remission - &gt;2≤4weeks</b>												
1	randomised trials	very serious <sup>7</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	48/97 (49.5%)	64/98 (65.3%)	RR 0.76 (0.59 to 0.97)	157 fewer per 1000 (from 20 fewer to 268 fewer)	⊕○○○ VERY LOW	IMPORTANT
<b>Adverse events</b>												
3	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	58/314 (18.5%)	62/292 (21.2%)	RR 0.89 (0.66 to 1.2)	23 fewer per 1000 (from 72 fewer to 42 more)	⊕⊕○○ LOW	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3,4</sup>	none	1/191 (0.52%)	1/182 (0.55%)	RR 0.95 (0.06 to 15.12)	0 fewer per 1000 (from 5 fewer to 78 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Evidence of single blinding.

<sup>2</sup> <sup>12</sup> >50% but <75%.

<sup>3</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>4</sup> Crosses the lower 0.75 relative risk (RR) MID.

<sup>5</sup> Single or unblinded studies. Overall unclear method of randomisation and allocation concealment.

<sup>6</sup> Single blinding, overall unclear method of randomisation and allocation concealment. Missing data is >10% difference in the treatment arms.

<sup>7</sup> Open study. Overall unclear method of randomisation and allocation concealment.

### Subgroup analysis

High heterogeneity values were found for the topical ASA versus topical ASAs preparation comparison (foam versus liquid enema) for clinical remission at 0≤2 weeks and >2≤4 weeks (73% and 70% respectively). Sensitivity analysis was carried out on the specified subgroups. None of which were found to explain the heterogeneity. See Table 15 and Table 16 for the study differences.

**Table 15: Topical aminosalicylates versus topical aminosalicylates (foam versus liquid enema): Clinical remission at 0≤2 weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
CAMPIERI1993 (mild)	2g	Mild	Proctosigmoiditis or distal (but included some patients with left sided UC) 91% rectum/sigmoid 9% left colon	N/A	18-75 years
CAMPIERI1993 (moderate)	4g	Moderate	Proctosigmoiditis or distal (but included some patients with left sided UC) 55% rectum/sigmoid 45% left colon	N/A	18-75 years
CORTOT2008	1g	no upper limit given (CAI≥4)	Up to the splenic flexure 44% proctitis 51% proctosigmoiditis 5% left sided	N/A	>18 years

**Table 16: Topical aminosalicylates versus topical aminosalicylates (foam versus liquid enema): endoscopic remission at >2≤4 weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
ARDIZZONE1999	4g	no upper limit given (CAI≥4 and EI≥6)	Up to the splenic flexure 25% proctitis 56% proctosigmoiditis 19% left sided	N/A	18-70 years



Study	Dose (per day)	Severity	Extent	Preparation	Age
CAMPIERI1993 (mild)	2g	Mild	Proctosigmoiditis or distal (but included some patients with left sided UC) 91% rectum/sigmoid 9% left colon	N/A	18-75 years
CAMPIERI1993 (moderate)	4g	Moderate	Proctosigmoiditis or distal (but included some patients with left sided UC) 55% rectum/sigmoid 45% left colon	N/A	18-75 years
CORTOT2008	1g	no upper limit given (CAI≥4)	Up to the splenic flexure 44% proctitis 51% proctosigmoiditis 5% left sided	N/A	>18 years

The four studies slightly differ in terms of different doses and severity, sensitivity analysis was carried out on the specified subgroups. This did not explain the heterogeneity. The CAMPIERI1993<sup>34</sup> and CORTOT2008<sup>43</sup> studies are single blind, with no other risks of bias identified. ARDIZZONE1999<sup>6</sup> is an open study, which had an unclear method of randomisation, allocation concealment and dropout rate. The treatment groups were also unbalanced for concurrent use of maintenance ASAs, which may explain some of the differences seen.

**Table 17: Suppository versus liquid enema**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Suppository	Liquid enema	Relative (95% CI)	Absolute		
Clinical remission - 0≤2weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	9/19 (47.4%)	8/20 (40%)	RR 1.18 (0.58 to 2.42)	72 more per 1000 (from 168 fewer to 568 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >2≤4 weeks												
1	randomised	serious <sup>1</sup>	no serious	no serious	very serious <sup>2,3</sup>	none	15/19	16/20	RR 0.99	8 fewer per 1000 (from	⊕○○○	CRITICAL

	trials		inconsistency	indirectness			(78.9%)	(80%)	(0.72 to 1.36)	224 fewer to 288 more)	VERY LOW	
<b>Clinical improvement - 0≤2 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	16/19 (84.2%)	17/20 (85%)	RR 0.99 (0.76 to 1.3)	8 fewer per 1000 (from 204 fewer to 255 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/19 (89.5%)	18/20 (90%)	RR 0.99 (0.8 to 1.23)	9 fewer per 1000 (from 180 fewer to 207 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission - 0≤2 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	9/19 (47.4%)	6/20 (30%)	RR 1.58 (0.7 to 3.59)	174 more per 1000 (from 90 fewer to 777 more)	⊕OOO VERY LOW	IMPORTANT
<b>Endoscopic remission - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	14/19 (73.7%)	13/20 (65%)	RR 1.13 (0.75 to 1.72)	84 more per 1000 (from 162 fewer to 468 more)	⊕OOO VERY LOW	IMPORTANT

<sup>1</sup> Evidence of angle blinding.

<sup>2</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>3</sup> Crosses the lower 0.75 relative risk (RR) MID.

### 5.4.3 Topical aminosaliclates versus topical aminosaliclates (dose comparison)

Table 18: Topical aminosaliclates dose comparisons

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose	Higher dose	Relative (95% CI)	Absolute		
Clinical remission: 1g versus 1.5g - 0≤2weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	13/32 (40.6%)	14/31 (45.2%)	RR 0.9 (0.51 to 1.59)	45 fewer per 1000 (from 221 fewer to 266 more)	⊕⊕OO LOW	CRITICAL
Clinical remission: 1g versus 1.5g - >2≤4 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	22/32 (68.8%)	23/31 (74.2%)	RR 0.93 (0.68 to 1.27)	52 fewer per 1000 (from 237 fewer to 200 more)	⊕⊕OO LOW	CRITICAL

<b>Clinical remission: 1g versus 2g - 0≤2weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	9/27 (33.3%)	11/30 (36.7%)	RR 0.91 (0.45 to 1.85)	33 fewer per 1000 (from 202 fewer to 312 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 1g versus 2g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	17/27 (63%)	20/30 (66.7%)	RR 0.94 (0.64 to 1.39)	40 fewer per 1000 (from 240 fewer to 260 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 1g versus 2g - &gt;6≤8weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	34/73 (46.6%)	35/71 (49.3%)	RR 0.94 (0.67 to 1.33)	30 fewer per 1000 (from 163 fewer to 163 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 1g versus 4g - 0≤2weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	9/27 (33.3%)	13/29 (44.8%)	RR 0.74 (0.38 to 1.45)	117 fewer per 1000 (from 278 fewer to 202 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 1g versus 4g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	17/27 (63%)	21/29 (72.4%)	RR 0.87 (0.6 to 1.25)	94 fewer per 1000 (from 290 fewer to 181 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 1g versus 4g -&gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	34/73 (46.6%)	32/73 (43.8%)	RR 1.06 (0.74 to 1.52)	26 more per 1000 (from 114 fewer to 228 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 2g versus 4g - 0≤2weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	11/30 (36.7%)	13/29 (44.8%)	RR 0.82 (0.44 to 1.52)	81 fewer per 1000 (from 251 fewer to 233 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 2g versus 4g -&gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	20/30 (66.7%)	21/29 (72.4%)	RR 0.92 (0.66 to 1.29)	58 fewer per 1000 (from 246 fewer to 210 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission: 2g versus 4g - &gt;6≤8weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	35/71 (49.3%)	32/73 (43.8%)	RR 1.12 (0.79 to 1.6)	53 more per 1000 (from 92 fewer to 263 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical improvement: 1g versus 1.5g - 0≤2weeks</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	24/32 (75%)	26/31 (83.9%)	RR 0.89 (0.69 to 1.15)	92 fewer per 1000 (from 260 fewer to 126 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Clinical improvement: 1g versus 1.5g - &gt;2≤4 weeks</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	26/32 (81.3%)	28/31 (90.3%)	RR 0.9 (0.73 to 1.1)	90 fewer per 1000 (from 244 fewer to 90 more)	⊕⊕⊕○ MODERATE	CRITICAL

<b>Clinical improvement: 1g versus 2g - 0≤2weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	21/27 (77.8%)	23/30 (76.7%)	RR 1.01 (0.77 to 1.35)	8 more per 1000 (from 176 fewer to 268 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement: 1g versus 2g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	23/27 (85.2%)	25/30 (83.3%)	RR 1.02 (0.82 to 1.28)	17 more per 1000 (from 150 fewer to 233 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement: 1g versus 2g - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	49/73 (67.1%)	46/71 (64.8%)	RR 1.04 (0.82 to 1.31)	26 more per 1000 (from 117 fewer to 201 more)	⊕OOO VERY LOW	CRITICAL
<b>Clinical improvement: 1g versus 4g - 0≤2weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	21/27 (77.8%)	24/29 (82.8%)	RR 0.94 (0.72 to 1.22)	50 fewer per 1000 (from 232 fewer to 182 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement: 1g versus 4g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/27 (85.2%)	25/29 (86.2%)	RR 0.99 (0.8 to 1.22)	9 fewer per 1000 (from 172 fewer to 190 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Clinical improvement: 1g versus 4g - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	49/73 (67.1%)	55/73 (75.3%)	RR 0.89 (0.72 to 1.1)	83 fewer per 1000 (from 211 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL
<b>Clinical improvement: 2g versus 4g - 0≤2weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	23/30 (76.7%)	24/29 (82.8%)	RR 0.93 (0.72 to 1.2)	58 fewer per 1000 (from 232 fewer to 166 more)	⊕⊕OO LOW	CRITICAL
<b>Clinical improvement: 2g versus 4g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/30 (83.3%)	25/29 (86.2%)	RR 0.97 (0.78 to 1.2)	26 fewer per 1000 (from 190 fewer to 172 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Clinical improvement: 2g versus 4g - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	46/71 (64.8%)	55/73 (75.3%)	RR 0.86 (0.69 to 1.07)	105 fewer per 1000 (from 234 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission: 1g versus 1.5g - &gt;2≤4 weeks</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	19/32 (59.4%)	17/31 (54.8%)	RR 1.08 (0.7 to 1.66)	44 more per 1000 (from 165 fewer to 362 more)	⊕⊕OO LOW	IMPORTANT
<b>Endoscopic remission: 1g versus 2g - 0≤2weeks</b>												
2	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	14/39 (35.9%)	13/43 (30.2%)	RR 1.18 (0.64 to 2.2)	54 more per 1000 (from 109 fewer to 363 more)	⊕OOO VERY LOW	IMPORTANT

<b>Endoscopic remission: 1g versus 2g - &gt;2≤4 weeks</b>												
2	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	21/39 (53.8%)	19/43 (44.2%)	RR 1.22 (0.78 to 1.89)	97 more per 1000 (from 97 fewer to 393 more)	⊕⊕⊕ LOW	IMPORTANT
<b>Endoscopic remission: 1g versus 2g - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	43/73 (58.9%)	46/71 (64.8%)	RR 0.91 (0.7 to 1.18)	58 fewer per 1000 (from 194 fewer to 117 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Endoscopic remission: 1g versus 4g - 0≤2 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	7/27 (25.9%)	11/29 (37.9%)	RR 0.68 (0.31 to 1.51)	121 fewer per 1000 (from 262 fewer to 193 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Endoscopic remission: 1g versus 4g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	12/27 (44.4%)	15/29 (51.7%)	RR 0.86 (0.5 to 1.49)	72 fewer per 1000 (from 259 fewer to 253 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Endoscopic remission: 1g versus 4g - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	43/73 (58.9%)	48/73 (65.8%)	RR 0.9 (0.7 to 1.15)	66 fewer per 1000 (from 197 fewer to 99 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Endoscopic remission: 2g versus 4g - 0≤2 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	9/30 (30%)	11/29 (37.9%)	RR 0.79 (0.39 to 1.62)	80 fewer per 1000 (from 231 fewer to 235 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Endoscopic remission: 2g versus 4g - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	13/30 (43.3%)	15/29 (51.7%)	RR 0.84 (0.49 to 1.44)	83 fewer per 1000 (from 264 fewer to 228 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Endoscopic remission: 2g versus 4g - &gt;6≤8 weeks</b>												
1	randomised trials	very serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	46/71 (64.8%)	48/73 (65.8%)	RR 0.99 (0.78 to 1.25)	7 fewer per 1000 (from 145 fewer to 164 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Clinical and endoscopic remission: 1g versus 2g - 0≤2 weeks</b>												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	3/12 (25%)	2/13 (15.4%)	RR 1.63 (0.33 to 8.11)	97 more per 1000 (from 103 fewer to 1000 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Clinical and endoscopic remission: 1g versus 2g - &gt;2≤4 weeks</b>												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	7/12 (58.3%)	4/13 (30.8%)	RR 1.9 (0.74 to 4.88)	277 more per 1000 (from 80 fewer to 1000 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Adverse events - 1g versus 1.5g</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	1/32 (3.1%)	0/31 (0%)	RR 2.91 (0.12 to 68.81)	-	⊕⊕⊕ LOW	IMPORTANT

Adverse events - 1g versus 2g												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	0/12 (0%)	1/13 (7.7%)	RR 0.36 (0.02 to 8.05)	49 fewer per 1000 (from 75 fewer to 542 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>2</sup> Crosses the lower 0.75 relative risk (RR) MID.

<sup>3</sup> Overall unclear method of randomisation and allocation concealment.

<sup>4</sup> Overall unclear method of randomisation and allocation concealment. Unclear drop out rate.

<sup>5</sup> Overall unclear method of randomisation and allocation concealment. Very limited baseline characteristics. Unclear if the clinical and endoscopic measures would have been validated.

#### 5.4.4 Topical aminosaliclates versus topical aminosaliclates (regimen comparison)

Table 19: Once versus twice a day regimen comparison

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Once a day	Twice a day	Relative (95% CI)	Absolute		
Clinical remission - >2≤4weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	21/44 (47.7%)	27/53 (50.9%)	RR 0.94 (0.62 to 1.41)	31 fewer per 1000 (from 194 fewer to 209 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >4≤6 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	34/44 (77.3%)	38/53 (71.7%)	RR 1.08 (0.85 to 1.36)	57 more per 1000 (from 108 fewer to 258 more)	⊕⊕○○ LOW	CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	24/44 (54.5%)	30/53 (56.6%)	RR 0.96 (0.67 to 1.38)	23 fewer per 1000 (from 187 fewer to 215 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Single blind.

<sup>2</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>3</sup> Crosses the lower 0.75 relative risk (RR) MID.

## 5.4.5 Topical aminosalicylates versus topical aminosalicylates (regimen and dose comparison)

Table 20: Once a day versus three times a day (different doses)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1g once a day	1.5g given three times a day	Relative (95% CI)	Absolute		
Clinical remission ->4≤6weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	168/201 (83.6%)	172/207 (83.1%)	RR 1.01 (0.92 to 1.1)	8 more per 1000 (from 66 fewer to 83 more)	⊕⊕⊕⊕ LOW	CRITICAL
Clinical improvement - >4≤6weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	186/201 (92.5%)	184/207 (88.9%)	RR 1.04 (0.98 to 1.11)	36 more per 1000 (from 18 fewer to 98 more)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - >4≤6weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	153/201 (76.1%)	164/207 (79.2%)	RR 0.96 (0.87 to 1.07)	32 fewer per 1000 (from 103 fewer to 55 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	38/201 (18.9%)	43/207 (20.8%)	RR 0.91 (0.62 to 1.35)	19 fewer per 1000 (from 79 fewer to 73 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Serious adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/201 (0.5%)	1/207 (0.48%)	RR 1.03 (0.06 to 16.35)	0 more per 1000 (from 5 fewer to 74 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Hospitalisations												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/201 (0.5%)	1/207 (0.48%)	RR 1.03 (0.06 to 16.35)	0 more per 1000 (from 5 fewer to 74 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Single blind. Unclear drop out rate.

<sup>2</sup> Crosses both the upper 1.25 and lower 0.75 relative risk (RR) MIDs.

## 5.5 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 5.6 Evidence statements

### 5.6.1 Clinical evidence statements

No quality of life evidence was identified for the topical reviews.

#### 5.6.1.1 Topical aminosalicylates versus placebo

##### Clinical remission

Topical ASAs are clinically more effective at increasing clinical remission rates compared to placebo at 2, 4, 6 and 8 weeks [moderate quality evidence, 4 studies, N=301; low quality evidence, 4 studies, N=301; low quality evidence, 1 study, N=111; low quality evidence, 1 study, N=277].

##### Clinical improvement

Topical ASAs are clinically more effective at increasing clinical improvement rates compared to placebo at 2, 4 [very low quality evidence, 5 studies, N=405; very low quality evidence, 5 studies, N=391] and 8 weeks [low quality evidence, 1 study, N=287] but not at 6 weeks [low quality evidence, 1 study, N=80].

##### Important outcomes

Topical ASAs are clinically more effective at increasing endoscopic remission rates compared to placebo [low to moderate quality evidence, 5 studies, N=588] at all time points apart from  $>4\leq 6$  weeks [1 study, N=111]. There was an unclear effect of topical ASAs increasing clinical and endoscopic remission rates, benefit was shown at  $>4\leq 6$  weeks (moderate quality evidence, 1 study, N=27] but there may be no clinically important difference at  $2\leq 4$  weeks [very low quality evidence, study, N=27]. There may be no clinically important difference in adverse events, serious adverse events and hospitalisation rates between topical ASAs and placebo [very low quality evidence, 2 studies, N=131; 1 study, N=111; 1 study, N=111].

#### 5.6.1.2 Preparation comparisons (foam versus liquid enemas)

##### Clinical remission

Foam enemas may be clinically more effective at increasing clinical remission rates compared to liquid enemas at  $0\leq 2$  weeks but there may be no clinically important difference at  $2\leq 4$  weeks [very low quality evidence, 3 studies, N=601; 3 studies, N=796].



### **Clinical improvement**

There was an unclear picture for clinical improvement. Foam enemas may be more clinically effective at increasing clinical improvement compared to liquid enemas at 0≤2 weeks but there may be no clinically important difference at 2≤4 or at > 6≤8 weeks [very low to moderate quality evidence, 1 study, N=233; 2 studies, N=281;1 study, N=48].

### **Important outcomes**

There may be no clinical difference in endoscopic remission rates between foam and liquid enemas, the direction of the estimate of effect favoured the liquid enema although liquid enemas may have a greater clinical and endoscopic remission rate compared to foam enemas at 2≤4 weeks [very low to low quality evidence, 3 studies, N=796;1 study, N=195]. There may be no clinically important difference in adverse or serious adverse event rates between foam and liquid enemas [very low to low quality evidence, 2 studies, N=606;1 study, N=373].

#### **5.6.1.3 Preparation comparisons (suppositories versus liquid enemas)**

##### **Clinical remission and clinical improvement**

There may be no clinical difference in clinical remission or clinical improvement rates between suppositories and liquid enemas [very low to low quality evidence, 1 study, N=39; 1 study, N=39].

##### **Important outcomes**

Suppositories may have a higher endoscopic remission rate compared to liquid enemas at 0≤2 weeks, but may not at 2≤4 weeks [very low quality evidence, 1 study, N=39].

#### **5.6.1.4 Dose comparisons**

##### **Clinical remission and clinical improvement**

There may be no clinical difference in clinical remission and clinical improvement rates between doses at all time points apart from at 0≤2 weeks (1g versus 4g) which favoured the higher dose for clinical remission rates [very low to low quality evidence, 1 study, N=63; 2 studies, N=211; 2 studies, N=202; 2 studies, N=203].

##### **Important outcomes**

There may be no clinically difference in endoscopic remission rates between doses apart from 1g versus 4g at 0≤2 weeks where the higher dose may be clinically more effective [low to very low quality evidence, 1 study, N=63; 3 studies, N=226; 2 studies, N=202; 2 studies, N=203]. Conversely there may be no clinical difference in clinical and endoscopic remission rates at 0≤2 weeks, but the lower dose of 1g may be clinically more effective at 2≤4 weeks compared to 2g [very low quality evidence, 1 study, N=25]. There may be no clinical difference in adverse events between doses [2 studies, N=88].

#### **5.6.1.5 Regimen comparison – once versus twice a day**

There may be no clinical difference in clinical remission rates or adverse events between once a day compared to twice a day [very low quality evidence, 1 study, N=97].

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

None of the outcomes identified (clinical remission, clinical improvement, endoscopic remission, adverse and serious adverse events and hospitalisations) showed a clinically important difference

between a regimen and dose comparison of once (1g) versus three times (1.5g) a day [very low to low quality evidence, 1 study, N=408].

### 5.6.2 Economic evidence statements

No relevant economic evaluations were identified.

## 5.7 Clinical evidence: Topical corticosteroids

Eight studies were included in the review.<sup>11,53,78,86,127,129,166,208</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

The reviews in this section are topical corticosteroids versus placebo (section 5.8.1) and topical corticosteroids versus topical corticosteroids (preparation comparison (section 5.8.2), dose comparison (section 5.8.3), interclass comparison (section 5.8.4) and interclass and preparation comparison (section 5.8.5)).

## 5.8 Evidence profile

### 5.8.1 Topical corticosteroids versus placebo

Table 21: Topical corticosteroids versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical steroids	Placebo	Relative (95% CI)	Absolute		
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission (>4≤6 weeks)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	46/114 (40.4%)	9/57 (15.8%)	RR 2.56 (1.35 to 4.85)	246 more per 1000 (from 55 more to 608 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission (>4≤6weeks)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	26/114 (22.8%)	2/57 (3.5%)	RR 6.5 (1.6 to 26.43)	193 more per 1000 (from 21 more to 892 more)	⊕○○○ VERY LOW	IMPORTANT
Serious Adverse Events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	none	3/114 (2.6%)	4/57 (7%)	RR 0.38 (0.09 to 1.62)	44 fewer per 1000 (from 64 fewer to 44 more)	⊕○○○ VERY LOW	IMPORTANT

1 Overall unclear method of randomisation and allocation concealment. Missing data >10% between treatment arms.

2 Risk of indirect population due to unclear severity of disease.

3 The 95% CI crosses both the lower 0.75 and upper 1.25 MIDs.

**Additional information which could not be meta-analysed:**

**Adverse events**

- HANAUER1998A: The most frequently reported adverse events were headache, back pain, dyspepsia and nausea. Only the drug related adverse events were reported which were 20/54 (37%) for the 2mg budesonide liquid enema group, 24/60 (40%) for the 8mg group and 18/57 (32%) for the placebo group.

## 5.8.2 Topical corticosteroids versus topical corticosteroids (preparation comparison)

Table 22: Foam versus liquid enema

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Foam enema	Liquid enema	Relative (95% CI)	Absolute		
Clinical remission (>2≤4 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	151/265 (57%)	174/268 (64.9%)	RR 0.88 (0.77 to 1.01)	78 fewer per 1000 (from 149 fewer to 6 more)	⊕⊕⊕ LOW	CRITICAL
Clinical improvement (>2≤4 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	177/210 (84.3%)	205/239 (85.8%)	RR 0.98 (0.91 to 1.06)	17 fewer per 1000 (from 77 fewer to 51 more)	⊕⊕⊕ LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission (>2≤4 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	106/204 (52%)	127/234 (54.3%)	RR 0.96 (0.8 to 1.14)	22 fewer per 1000 (from 109 fewer to 76 more)	⊕⊕⊕ LOW	IMPORTANT
Adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	86/267 (32.2%)	87/268 (32.5%)	RR 0.99 (0.78 to 1.27)	3 fewer per 1000 (from 71 fewer to 88 more)	⊕⊕⊕ VERY LOW	IMPORTANT
Serious Adverse Events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>4</sup>	none	2/267 (0.75%)	4/268 (1.5%)	RR 0.5 (0.09 to 2.72)	7 fewer per 1000 (from 14 fewer to 26 more)	⊕⊕⊕ VERY LOW	IMPORTANT

1 Overall unclear method of randomisation and allocation concealment. Unclear drop out rate. Double blind but no further information given.

2 Risk of an indirect population as there was no upper limit on the severity inclusion criteria.

3 Crosses the upper 1.25 relative risk (RR) MID.

4 Crosses both the lower 0.75 and upper 1.25 relative risk (RR) MIDs.

### 5.8.3 Topical corticosteroids versus topical corticosteroids (dose comparison)

**Table 23: Budesonide dose comparison**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose	Higher dose	Relative (95% CI)	Absolute		
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission >4≤6weeks - 2mg budesonide versus 8mg budesonide												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	19/54 (35.2%)	27/60 (45%)	RR 0.78 (0.49 to 1.24)	99 fewer per 1000 (from 229 fewer to 108 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission (in weeks) - >2≤4 weeks (2mg vs 4mg budesonide)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	24/73 (32.9%)	31/76 (40.8%)	RR 0.81 (0.53 to 1.23)	77 fewer per 1000 (from 192 fewer to 94 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission (in weeks) - >4≤6 weeks (2mg versus 8mg budesonide)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	10/54 (18.5%)	16/60 (26.7%)	RR 0.69 (0.35 to 1.4)	83 fewer per 1000 (from 173 fewer to 107 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission (in weeks) - >6≤8 weeks (2mg vs 4mg of budesonide)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	37/73 (50.7%)	41/76 (53.9%)	RR 0.94 (0.69 to 1.28)	32 fewer per 1000 (from 167 fewer to 151 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events - 2mg budesonide versus 4mg budesonide												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	48/73 (65.8%)	54/76 (71.1%)	RR 0.93 (0.74 to 1.15)	50 fewer per 1000 (from 185 fewer to 107 more)	⊕○○○ VERY LOW	IMPORTANT
Serious Adverse Events - 2mg budesonide versus 8mg budesonide												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	0/54 (0%)	3/60 (5%)	RR 0.16 (0.01 to 3)	42 fewer per 1000 (from 49 fewer to 100 more)	⊕○○○ VERY LOW	IMPORTAN

1 Overall unclear method of randomisation and allocation concealment. Very limited baseline characteristics. Double blind but no further information given.

2 Risk of an indirect population due to unclear severity of disease.

3 The 95% CI Crosses the lower 0.75 relative risk (RR) MID.

4 The 95% CI Crosses the upper 1.25 relative risk (RR) MID.

#### 5.8.4 Topical corticosteroids versus topical corticosteroids (interclass comparisons)

**Table 24: Budesonide foam enema versus hydrocortisone foam enema**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide foam enema	Hydrocortisone foam enema	Relative (95% CI)	Absolute		
Clinical remission (>6≤8 weeks)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	64/120 (53.3%)	67/128 (52.3%)	RR 1.02 (0.81 to 1.29)	10 more per 1000 (from 99 fewer to 152 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>4</sup>	none	36/120 (30%)	50/128 (39.1%)	RR 0.77 (0.54 to 1.09)	90 fewer per 1000 (from 180 fewer to 35 more)	⊕○○○ VERY LOW	IMPORTANT
Serious Adverse Events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	1/120 (0.83%)	4/128 (3.1%)	RR 0.27 (0.03 to 2.35)	23 fewer per 1000 (from 30 fewer to 42 more)	⊕○○○ VERY LOW	IMPORTANT

1 Open study. Overall unclear method of randomisation and allocation concealment. Unclear drop out rate.

2 Risk of an indirect population due to there being no upper limit for the severity of disease.

3 95% CI Crosses the upper 1.25 relative risk (RR) MID.

4 95% CI Crosses the lower 0.75 relative risk (RR) MID.

**Table 25: Budesonide versus prednisolone**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide liquid enema	Prednisolone liquid enema	Relative (95% CI)	Absolute		

<b>Clinical remission</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Clinical improvement</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission - &gt;2≤4 weeks (fixed effects)</b>												
2	randomised trials	very serious <sup>1</sup>	very serious <sup>2</sup>	serious <sup>3</sup>	very serious <sup>4,5</sup>	none	23/76 (30.3%)	22/88 (25%)	RR 1.19 (0.72 to 1.97)	48 more per 1000 (from 70 fewer to 243 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Endoscopic remission - &gt;2≤4 weeks (random effects)</b>												
2	randomised trials	very serious <sup>1</sup>	very serious <sup>2</sup>	serious <sup>3</sup>	very serious <sup>4,5</sup>	none	23/76 (30.3%)	22/88 (25%)	RR 1.16 (0.34 to 3.97)	40 more per 1000 (from 165 fewer to 743 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Endoscopic remission - &gt;6≤8 weeks</b>												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	serious <sup>3</sup>	serious <sup>4</sup>	none	18/45 (40%)	28/55 (50.9%)	RR 0.79 (0.5 to 1.22)	107 fewer per 1000 (from 255 fewer to 112 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Clinical and endoscopic remission -&gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	serious <sup>3</sup>	very serious <sup>4,5</sup>	none	7/45 (15.6%)	13/55 (23.6%)	RR 0.66 (0.29 to 1.51)	80 fewer per 1000 (from 168 fewer to 121 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Clinical and endoscopic remission - &gt;6≤8 weeks</b>												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	serious <sup>3</sup>	serious <sup>4</sup>	none	16/45 (35.6%)	26/55 (47.3%)	RR 0.75 (0.46 to 1.22)	118 fewer per 1000 (from 255 fewer to 104 more)	⊕○○○ VERY LOW	IMPORTANT

1 Single investigator blind. Very limited baseline characteristics. Overall unclear method of randomisation and allocation concealment.

2  $I^2 > 75\%$ .

3 Risk of an indirect population due to unclear severity of disease.

4 95% CI Crosses the lower 0.75 relative risk (RR) MID.

5 95% CI Crosses the upper 1.25 relative risk (RR) MID.

6 Single investigator blind. Very limited baseline characteristics.

#### Additional information which could not be meta-analysed:

#### Adverse events

LOFTBERG1994: No data were given for adverse events but it was reported that there were slightly more events in the budesonide group. Many were gastrointestinal complaints (mild) and two patients got acne (1 in each treatment group).

### Subgroup analysis

A high heterogeneity value was found (81%) for the budesonide enema versus prednisolone disodium phosphate enema comparison and endoscopic remission at >2≤4 weeks outcome. See Table 26 for the study differences. Sensitivity analysis on the subgroups did not explain the heterogeneity.

**Table 26: Budesonide enema versus prednisolone enema: endoscopic remission at >2≤4 weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
DANIELSSON1987	2mg budesonide enema 31.25mg prednisolone enema	Unclear. No inclusion criteria set and no baseline characteristic data	“distal” but no definition given	Liquid enemas	16-65 years
LOFTBERG1994	2.3mg budesonide 31.25mg prednisolone	Unclear. No inclusion criteria set and no baseline characteristic data	Up to the splenic flexure	Liquid enemas	>18 years

Both studies<sup>53,129</sup> are single blind and have very limited baseline characteristics recorded. LOFTBERG1994<sup>129</sup> has a dropout rate of 22% (<10% difference between each treatment arm) and no data on how many were on maintenance therapy. DANIELSSON1987<sup>53</sup> has an unclear method of randomisation and allocation concealment. Both studies use the definition of a grade of 0 for endoscopic remission and use the same indexes to measure it (According to Truelove & Richards. See the evidence tables for further detail).

**Table 27: Budesonide versus methylprednisolone**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide liquid enema	Methylprednisolone liquid enema	Relative (95% CI)	Absolute		
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL



Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Hospitalization												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/44 (0%)	1/44 (2.3%)	RR 0.33 (0.01 to 7.97)	15 fewer per 1000 (from 22 fewer to 158 more)	⊕○○○ VERY LOW	IMPORTANT

1 Single blind.

2 95% CI crosses both the lower 0.75 and upper 1.25 relative risk (RR) MIDs.

### 5.8.5 Topical corticosteroids versus topical corticosteroids (interclass and preparation comparison)

**Table 28: Budesonide liquid enema versus hydrocortisone foam enema**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Budesonide liquid enema	Hydrocortisone foam enema	Relative (95% CI)	Absolute		
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission (>2≤4weeks)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	22/36 (61.1%)	17/35 (48.6%)	RR 1.26 (0.82 to 1.93)	126 more per 1000 (from 87 fewer to 452 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	8/37 (21.6%)	9/35 (25.7%)	RR 0.84 (0.37 to 1.93)	41 fewer per 1000 (from 162 fewer to 239 more)	⊕○○○ VERY LOW	IMPORTANT

1 Single investigator blind. Overall unclear method of randomisation and allocation concealment.

2 Risk of an indirect population due to the risk of including patients with severe disease.

3 95% CI Crosses the upper 1.25 relative risk (RR) MID.

4 95% CI Crosses the lower 0.75 relative risk (RR) MID.

## 5.9 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 5.10 Evidence statements

### 5.10.1 Clinical evidence statements

#### 5.10.1.1 Topical corticosteroids versus placebo

No evidence was identified for clinical remission, improvement or quality of life.

#### Important outcomes

Topical steroids are more clinically effective at increasing endoscopic and clinical and endoscopic remission rates compared to placebo [very low quality evidence, 1 study, N=171]. There may be no clinical difference in serious adverse events between topical steroids and placebo [very low quality evidence, 1 study, N=171].

#### 5.10.1.2 Preparation comparison

There is no clinically important difference in clinical remission or clinical improvement rates between foam and liquid steroid enemas at 2≤4 weeks [Low quality evidence, 1 study, N=533; N=449].

#### Important outcomes

There is no clinically important difference in endoscopic remission rates (>2≤4 weeks) or in adverse or serious adverse event rates between foam and liquid steroid enemas [very low to low quality evidence, 1 study, N=438; 1 study, N=535; 1 study, N=535].

#### 5.10.1.3 Dose comparison

No evidence was identified for clinical remission, improvement or quality of life.

#### Important outcomes

There may be no clinical difference in increasing endoscopic, clinical and endoscopic remission or in adverse or serious adverse event rates between any of the budesonide enemas doses, [very low quality evidence, 1 study, N=114; 1 study, N=149; 1 study, N=114].

#### **5.10.1.4 Interclass comparison**

##### **Budesonide and hydrocortisone foam enemas**

###### **Clinical remission**

There may be no clinical difference in clinical remission rates between budesonide and hydrocortisone foam enemas at  $>6\leq 8$  weeks [very low quality evidence, 1 study, N=248].

No evidence was identified for clinical improvement rates.

###### **Important outcomes**

There may be no clinical difference in adverse and serious adverse event rates between budesonide and hydrocortisone foam enemas at  $>6\leq 8$  weeks, the direction of the estimate of effect favoured less events with budesonide [very low quality evidence, 1 study, N=248].

##### **Budesonide and prednisolone disodium phosphate liquid enemas**

No evidence was identified for clinical remission, clinical improvement or quality of life.

###### **Important outcomes**

Very low quality evidence showed there may be no clinical difference in endoscopic or clinical and endoscopic remission rates between budesonide and prednisolone disodium phosphate enemas at  $>2\leq 4$  or  $>6\leq 8$  weeks [very low quality evidence, 2 studies, N=164; 1 study, N=100; 1 study, N=100; 1 study, N=100].

##### **Budesonide and methylprednisolone liquid enemas**

No evidence was identified for clinical remission, clinical improvement or quality of life.

###### **Hospitalizations**

There may be no clinical difference in hospitalization rates between budesonide and methylprednisolone enemas at  $2\leq 4$  weeks [very low quality evidence, 1 study, N=88].

#### **5.10.1.5 Interclass and preparation comparison**

##### **Budesonide liquid enema versus hydrocortisone foam enema**

No evidence was identified for clinical remission, clinical improvement or quality of life.

###### **Important outcomes**

There may be no clinical difference in endoscopic remission rates or in adverse event rates between budesonide liquid enemas and hydrocortisone foam enemas at  $2\leq 4$  weeks [very low quality evidence, 1 study, N=71].

#### **5.10.2 Economic evidence statements**

- No relevant economic evaluations were identified.

## **5.11 Clinical evidence: Topical aminosalicylates versus topical corticosteroids**

Eight studies were included in the review.<sup>19,63,70,89,119-121,147</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

## 5.12 Evidence profile

### 5.12.1 Topical aminosalicylates versus topical corticosteroids

Table 29: Topical aminosalicylates versus topical corticosteroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical ASAs	Topical Steroids	Relative (95% CI)	Absolute		
Clinical Remission 0≤2 weeks												
2	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	38/97 (39.2%)	25/99 (25.3%)	RR 1.59 (1.05 to 2.40)	149 more per 1000 (from 13 more to 354 more)	⊕○○○ VERY LOW	CRITICAL
Clinical Remission> 2≤4 weeks, random effects												
>6	randomised trials	very serious <sup>1,3</sup>	serious <sup>4</sup>	serious <sup>5</sup>	serious <sup>2</sup>	none	211/360 (58.6%)	151/353 (42.8%)	RR 1.30 (1.00 to 1.69)	128 more per 1000 (from 0 more to 295 more)	⊕○○○ VERY LOW	CRITICAL
Clinical Remission >6≤8 weeks												
1	randomised trials	serious <sup>5</sup>	no serious inconsistency	serious <sup>5</sup>	serious <sup>2</sup>	none	82/106 (77.4%)	65/101 (64.4%)	RR 1.2 (1.01 to 1.44)	129 more per 1000 (from 6 more to 283 more)	⊕○○○ VERY LOW	CRITICAL
Clinical Improvement 0≤2 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	32/56 (57.1%)	33/61 (54.1%)	RR 1.06 (0.76 to 1.46)	32 more per 1000 (from 130 fewer to 249 more)	⊕○○○ VERY LOW	CRITICAL
Clinical Improvement >2≤4 weeks, random effects												
2	randomised trials	serious <sup>8</sup>	very serious inconsistency <sup>11</sup>	no serious indirectness	very serious <sup>2,7</sup>	none	18/24 (75%)	13/23 (56.5%)	RR 1.62 (0.37 to 7.06)	350 more per 1000 (from 356 fewer to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Quality of Life >2≤4 weeks (Better indicated by lower values)												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	serious <sup>5</sup>	serious <sup>9</sup>	none	60	63	-	MD 7.2 higher (3.27 lower to 17.67 higher)	⊕○○○ VERY LOW	CRITICAL
Quality of Life >6≤8 weeks (Better indicated by lower values)												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	serious	serious <sup>9</sup>	none	66	65	-	MD 7.1 higher (3.12 lower to 17.32 higher)	⊕○○○ VERY LOW	CRITICAL
Endoscopic Remission 0≤2 weeks												

1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,7</sup>	none	17/56 (30.4%)	15/61 (24.6%)	RR 1.23 (0.68 to 2.23)	57 more per 1000 (from 79 fewer to 302 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Endoscopic Remission &gt;2≤4 weeks</b>												
3	randomised trials	very serious <sup>1,10</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	68/204 (33.3%)	51/199 (25.6%)	RR 1.30 (0.97 to 1.75)	77 more per 1000 (from 8 fewer to 192 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Endoscopic Remission &gt;6≤8 weeks</b>												
1	randomised trials	serious <sup>5</sup>	no serious inconsistency	serious <sup>5</sup>	no serious imprecision	none	76/106 (71.7%)	76/103 (73.8%)	RR 0.97 (0.82 to 1.15)	22 fewer per 1000 (from 133 fewer to 111 more)	⊕⊕○○ LOW	IMPORTANT
<b>Clinical and Endoscopic Remission 0≤2 weeks</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,7</sup>	none	15/56 (26.8%)	12/61 (19.7%)	RR 1.36 (0.7 to 2.65)	71 more per 1000 (from 59 fewer to 325 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Clinical and Endoscopic Remission &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	serious <sup>7</sup>	none	3/13 (23.1%)	8/11 (72.7%)	RR 0.32 (0.11 to 0.91)	495 fewer per 1000 (from 65 fewer to 647 fewer)	⊕⊕○○ LOW	IMPORTANT
<b>Adverse events</b>												
6	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	serious <sup>5</sup>	serious <sup>2</sup>	none	109/410 (26.6%)	93/405 (23%)	RR 1.16 (0.92 to 1.48)	37 more per 1000 (from 18 fewer to 110 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Serious adverse events</b>												
2	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	serious <sup>5</sup>	very serious <sup>2,7</sup>	none	3/166 (1.8%)	2/163 (1.2%)	RR 1.47 (0.25 to 8.63)	6 more per 1000 (from 9 fewer to 94 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Hospitalisations</b>												
2	randomised trials	serious <sup>6,8</sup>	no serious inconsistency	serious <sup>5</sup>	very serious <sup>2,7</sup>	none	2/128 (1.6%)	3/127 (2.4%)	RR 0.66 (0.12 to 3.79)	8 fewer per 1000 (from 21 fewer to 66 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Colectomy</b>												
1	randomised trials	serious <sup>8</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,7</sup>	none	0/9 (0%)	1/9 (11.1%)	OR <sup>12</sup> 0.14 (0 to 6.82)	94 fewer per 1000 (from 111 fewer to 349 more) <sup>13</sup>	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Overall unclear dropout rate or >10% difference in missing data between the treatment arms.

<sup>2</sup> 95% CI Crosses the upper 1.25 relative risk (RR) MID.

<sup>3</sup> Single blind and open studies.

<sup>4</sup>  $I^2$  <50% but <75%.

<sup>5</sup> Risk of an indirect population due to severity of disease.

<sup>6</sup> Open study.

<sup>7</sup> 95% CI Crosses the lower 0.75 relative risk (RR) MID.

<sup>8</sup> Overall unclear method of randomisation and allocation concealment.

<sup>9</sup> Crosses the upper MID of 16.3 (0.5 x baseline control SD)

<sup>10</sup> Single blind.

<sup>11</sup>  $I^2 > 75\%$ .

<sup>12</sup> Peto odds ratio

<sup>13</sup> Risk difference

### Subgroup analysis

A high heterogeneity value was found (57%) between six studies<sup>63,70,89,119-121</sup> for clinical remission at  $>2\leq 4$  weeks. Given the variation in drug dose, type and preparation, and because of indiscernible differences in the populations, there were no obvious subgroups that could be pooled and explained the heterogeneity.

**Table 30: Topical 5-ASAs versus topical corticosteroids: clinical remission at  $>2\leq 4$  weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
FARUP1995	1g mesalazine (Mesasal) 178mg x2 Hydrocortisone (Colifoam)	Not clear, DAI>6	Proctitis Proctosigmoiditis	ASA – suppositories Steroid – foam enema	17-70 years
FRIEDMAN1986A	4g 5-ASA (unknown type) 100mg hydrocortisone	Mild to moderate	At least 5cm and no more than 60cm from anal verge	ASA – liquid enema Steroid – liquid enema	$\geq 18$ years
HARTMAN2010	4g mesalazine (Salofalk) 2mg Budesonide (Entocort)	Mild to moderate, CAI>4, EI>2	Left-sided	ASA- liquid enema Steroid – liquid enema	18- 70 years
LAURITSEN1986	1g mesalazine (Pentasa) 25mg Prednisolone	Mild to moderate (Binder scale)	Sigmoid colon or rectum or both	ASA – liquid enema Steroid – liquid enema	18-66 years
LEE1996	2g mesalazine (unknown) 20mg Prednisolone	Not described	Not beyond splenic flexure	ASA- foam enema Steroid - foam enema	$\geq 18$ years
LEMANN1995	1g mesalazine (Pentasa) 2mg Budesonide (Entocort)	Not clear	Not beyond splenic flexure	ASA- liquid enema Steroid – liquid enema	$\geq 18$ years

Heterogeneity was also found between MULDER1988<sup>147</sup> and FRIEDMAN1986A<sup>70</sup> for clinical improvement at  $>2\leq 4$  weeks. See Table 31 for the study differences. The heterogeneity could be due to the type of rectal steroid used and their doses.

**Table 31: Topical aminosalicylates versus topical corticosteroids: clinical improvement at >2≤4 weeks**

Study	Dose (per day)	Severity	Extent	Preparation	Age
FRIEDMAN1986A	4g 5-ASA (unknown type) 100mg hydrocortisone	Mild to moderate	At least 5cm and no more than 60cm from anal verge	ASA – liquid enema Steroid – liquid enema	≥18 years
MULDER1988	3g 5-ASA (unknown type) 30mg prednisolone	Mild to moderate	Distal 20cm of the colon	ASA- liquid enema Steroid – liquid enema	21-74 years



## 5.13 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 5.14 Evidence statements

### 5.14.1 Clinical evidence statements

#### Clinical remission and clinical improvement

Topical ASAs may be more clinically effective at increasing clinical remission rates ( $0 \leq 2$ ,  $2 < 4$  and  $6 \leq 8$  weeks) and clinical improvement rates ( $2 < 4$  weeks) compared to topical steroids [very low quality evidence, 2 studies, N=196; 6 studies, N=713; 1 study, N=207; 2 studies, N=47]. There may be no clinical difference between topical ASAs and topical steroids in clinical improvement rates at  $0 \leq 2$  weeks [very low quality evidence, 1 study, N=117]

#### Quality of life

There may be no clinical difference between topical ASAs and topical steroids in quality of life scores at  $2 \leq 4$  and  $6 \leq 8$  weeks [very low quality evidence, 1 study, N=123; 1 study, N=131].

#### Important outcomes

There may be no clinical difference between topical ASAs and topical steroids in endoscopic ( $0 \leq 2$ ,  $2 \leq 4$  and  $6 \leq 8$  weeks) or clinical and endoscopic remission rates ( $0 \leq 2$  weeks) [very low quality evidence, 1 study, N=117; 3 studies, N=403; 1 study, N=209]. Topical steroids may be more clinically effective at increasing clinical and endoscopic remission rates at  $2 \leq 4$  weeks [1 study, N=24]. There may be no clinical difference between topical ASAs and topical steroids in adverse, serious adverse, hospitalisation event or colectomy rates [very low quality evidence, 6 studies, N=815; 2 studies, N=329; 2 studies, N=255; 1 study, N=18].

### 5.14.2 Economic evidence statements

No relevant economic evaluations were identified.

## 5.15 Clinical evidence: Oral aminosalicylates

Thirty-seven studies that compared oral ASA treatments with placebo or to each other were included<sup>27,50,57,62,66-68,71,76,82,85,87,88,95,97,100,102,104,107,112,115,123,125,135,141,142,172,173,176,181,189,190,193,196,197,203,232</sup>.

One of these studies<sup>66</sup> was a paediatric study.

The BNF states that: The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable. In order to address this, mesalazines were

compared to each other where possible and disease extent was explored where heterogeneity was present. The oral mesalazines listed in the BNF are Asacol, Ipocol, Mesren, Mezavant, Octasa, Pentasa and Salofalk. The reviews in this guideline name the mesalazine as it is named in the studies. We are aware that the mesalazines can change brand names, for example Mesren was been rebranded as Octasa 400 in December 2012.

The mesalazines were also compared to the aminosalicylates where possible. The mesalazines named in the included studies were Asacol, Ipocol, mesalazine (Eudragit-L coated; Ethylcellulose coated), Mezavant XL, Pentasa and Salofalk. The other aminosalicylates in the included studies were balsalazide, olsalazine and sulphasalazine.

The reviews in this section are oral aminosalicylates versus placebo (section 5.16.1) and oral aminosalicylates versus oral aminosalicylates (dose comparison (section 5.16.2), mesalazine comparison (section 5.16.3) and aminosalicylates comparison (section 5.16.4)).

Evidence from the studies are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

“Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis” was published by the Cochrane collaboration in 1997 and was updated in 2006, 2010 and 2012<sup>64</sup>. The review included 48 studies which compared oral 5-ASA treatment to placebo, sulphasalazine or other oral 5-ASAs. The Cochrane review concluded 5-ASA was superior to placebo and no more effective than sulphasalazine. Once daily dosing appears to be as clinically effective as conventional dosing of 5-ASA. There does not appear to be any differences between the formulations. 2.4g daily dose appears to be effective for people with mild to moderately active ulcerative colitis, and that those with moderate disease may benefit from the higher dose of 4.8g. The Cochrane review was excluded as it included trials that compared doses of sulphasalazine that were under 4g which was considered inconsistent with clinical practice, and it also included treatments that are not available in the UK. The following studies included in the Cochrane review were excluded from the Ulcerative Colitis review for the following reasons:

- ANDREOLI 1987; BRESCI1990; GREEN2002; MAIER1985; MANSFIELD2002; MUNAKATA 1995; QIAN2004; RACHMILEWITZ1989; RAO1989; RILEY1988; TURS12004; WILLOUGHBY1988 : below recommended dosing as per the BNF
- FLEIG1998: benzalazine (SAB) not available in the UK
- GOOD1992; SUTHERLAND1990: Rowasa not available in the UK
- KRUIS1998: Claversal not available in the UK
- EWE1988: Cross-over trial, results only given at the end of the trial
- CAI2001: Study is in Chinese. Insufficient details in the Cochrane review to include the study; no trial duration, no extent of disease, no definition of clinical improvement.

## 5.16 Evidence profile

### 5.16.1 Oral aminosalicylates versus placebo

**Table 32: Oral aminosalicylates versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA	Placebo	Relative (95% CI)	Absolute		
Clinical remission - >2 weeks ≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	2/106 (1.9%)	1/52 (1.9%)	RR 0.98 (0.09 to 10.57)	0 fewer per 1000 (from 18 fewer to 184 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >4weeks ≤6 weeks												
2	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	22/155 (14.2%)	4/90 (4.4%)	RR 3.37 (1.2 to 9.43)	105 more per 1000 (from 9 more to 375 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >6weeks ≤8 weeks												
6	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	379/1107 (34.2%)	88/497 (17.7%)	RR 1.89 (1.53 to 2.33)	158 more per 1000 (from 94 more to 235 more)	⊕⊕○○ LOW	CRITICAL
Clinical remission - >8 weeks												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	27/183 (14.8%)	12/90 (13.3%)	RR 1.11 (0.59 to 2.08)	15 more per 1000 (from 55 fewer to 144 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - >2 weeks ≤4 weeks												
6	randomised trials	very serious <sup>6</sup>	no serious inconsistency	serious <sup>7</sup>	no serious imprecision	none	92/230 (40%)	41/170 (24.1%)	RR 1.98 (1.46 to 2.68)	236 more per 1000 (from 111 more to 405 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - >4 weeks ≤6 weeks												
3	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/170 (38.2%)	17/105 (16.2%)	RR 2.50 (1.57 to 3.98)	243 more per 1000 (from 92 more to 482 more)	⊕⊕○○ LOW	CRITICAL
Clinical improvement - >6 weeks ≤8 weeks												
6	randomised trials	very serious <sup>6</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	649/1107 (58.6%)	177/497 (35.6%)	RR 1.59 (1.40 to 1.80)	210 more per 1000 (from 142 more to 285 more)	⊕⊕○○ LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	0%	-	-		CRITICAL
Endoscopic remission - >6 weeks ≤8 weeks												

3	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	354/613 (57.7%)	95/259 (36.7%)	RR 1.53 (1.29 to 1.82)	194 more per 1000 (from 106 more to 301 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Endoscopic remission - &gt;8 weeks</b>												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	73/183 (39.9%)	31/90 (34.4%)	RR 1.16 (0.83 to 1.62)	55 more per 1000 (from 59 fewer to 214 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Clinical and endoscopic remission - &gt;6 weeks ≤8 weeks</b>												
4	randomised trials	very serious <sup>8</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	202/722 (28%)	50/375 (13.3%)	RR 1.83 (1.38 to 2.43)	111 more per 1000 (from 51 more to 191 more)	⊕⊕○○ LOW	IMPORTANT
<b>Adverse events</b>												
9	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	511/996 (51.3%)	245/531 (46.1%)	RR 1.00 (0.90 to 1.11)	0 fewer per 1000 (from 46 fewer to 51 more)	⊕⊕○○ LOW	IMPORTANT
<b>Serious adverse events</b>												
5	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	32/944 (3.4%)	13/422 (3.1%)	RR 1.09 (0.58 to 2.06)	3 more per 1000 (from 13 fewer to 33 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of overall unclear blinding and unclear attrition rates.

<sup>2</sup> Crosses both the lower 0.75 and upper 1.25 relative risk (RR) MIDs.

<sup>3</sup> Limitations comprised of selection bias, unclear blinding and high attrition rates.

<sup>4</sup> Crosses the lower 1.25 relative risk (RR) t MID

<sup>5</sup> Limitations comprised of selection bias and high attrition rates.

<sup>6</sup> Limitations comprised of selection bias, unclear blinding, measurement bias and high attrition rates.

<sup>7</sup> Included people with severe disease in two studies.

<sup>8</sup> Limitations comprised of unclear blinding and high attrition rates.

#### Additional narrative information which could not be meta-analysed:

- Clinical improvement: No data were provided but FEURLE1989<sup>67</sup> described there to be no significant difference between the two groups for clinical score.
- Adverse events: The data in the HETZEL1986<sup>95</sup> paper reported the number of events, not the number of patients having one or more events. However the numbers were similar in each arm. In the ZINBERG1990<sup>232</sup> paper, it was unclear which arm the patients belonged to who had the adverse events. This included two patients withdrawing due to watery diarrhoea, transient diarrhoea (3 patients), rash (3 patients), transient flare of acne (2) and a recurrent anxiety attack (1 patient). HANAUER1993<sup>82</sup> report that the most frequently reported AEs were diarrhoea, headache, melena and abdominal pain of which they were all higher in the placebo group.

## 5.16.2 Oral aminosalicylates versus oral aminosalicylates (dose comparison)

**Table 33: Mesalazine (Pentasa)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Pentasa) lower dose	Mesalazine (Pentasa) higher dose	Relative (95% CI)	Absolute		
Clinical remission - 2g versus 4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	28/97 (28.9%)	28/95 (29.5%)	RR 0.98 (0.63 to 1.52)	6 fewer per 1000 (from 109 fewer to 153 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 2.25g versus 4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	9/59 (15.3%)	13/59 (22%)	RR 0.69 (0.32 to 1.49)	68 fewer per 1000 (from 150 fewer to 108 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 2g versus 4g												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	77/97 (79.4%)	80/95 (84.2%)	RR 0.94 (0.82 to 1.08)	51fewer per 1000 (from 152fewer to 67 more)	⊕⊕⊕○ MODERATE	CRITICAL
Clinical improvement - 2.25g versus 4g												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	27/59 (45.8%)	45/59 (76.3%)	RR 0.60 (0.44 to 0.82)	305 fewer per 1000 (from 137 fewer to 427 fewer)	⊕⊕○○ LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - 2g versus 4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	43/97 (44.3%)	46/95 (48.4%)	RR 0.92 (0.68 to 1.24)	39fewer per 1000 (from 155 fewer to 116 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events - 2g versus 4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	15/97 (15.5%)	19/95 (20%)	RR 0.77 (0.42 to 1.43)	46 fewer per 1000 (from 116 fewer to 86 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events - 2.25g versus 4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	52/63 (82.5%)	46/60 (76.7%)	RR 1.08 (0.9 to 1.29)	61 more per 1000 (from 77 fewer to 222 more)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events - 2g versus 4g												

1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	10/97 (10.3%)	4/95 (4.2%)	RR 2.45 (0.80 to 7.54)	61 more per 1000 (from 8 fewer to 275 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Serious adverse events - 2.25g versus 4g</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/63 (0%)	2/60 (3.3%)	RR 0.19 (0.01 to 3.89)	27 fewer per 1000 (from 33 fewer to 96 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Hospitalisations - 2.25g versus 4g</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/63 (0%)	1/60 (1.7%)	OR 0.13 (0 to 6.5) <sup>5</sup>	20 fewer per 1000 (from 60 fewer to 30 more) <sup>6</sup>	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias, unclear blinding and high attrition rates.

<sup>2</sup> Crosses both the 0.75 and 1.25 relative risk (RR) to MIDs.

<sup>3</sup> Crosses 0.75 relative risk (RR) to MID.

<sup>4</sup> Crosses 1.25 relative risk (RR) to MID.

<sup>5</sup> Peto odds ratio.

<sup>6</sup> Risk difference.

**Table 34: Mesalazine (Mezavant XL)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Mezavant XL) lower dose	Mesalazine (Mezavant XL) higher dose	Relative (95% CI)	Absolute		
Clinical remission - 1.2g versus 2.4g												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/13 (0%)	4/14 (28.6%)	RR 0.12 (0.01 to 2.02)	251 fewer per 1000 (from 283 fewer to 291 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 2.4g versus 4.8g												
3	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	72/186 (38.7%)	66/185 (35.7%)	RR 1.09 (0.84 to 1.42)	32 more per 1000 (from 57 fewer to 150 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 1.2g versus 4.8g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/13 (0%)	2/11 (18.2%)	RR 0.17 (0.01 to 3.23)	151 fewer per 1000 (from 180 fewer to 405 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 2.4g versus 4.8g												
2	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/172 (58.1%)	108/174 (62.1%)	RR 0.94 (0.79 to 1.11)	37 fewer per 1000 (from 130 fewer to 68 more)	⊕⊕⊕○ MODERATE	CRITICAL

Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - 2.4g versus 4.8g												
1	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	none	58/84 (69%)	66/85 (77.6%)	RR 0.89 (0.74 to 1.07)	85 fewer per 1000 (from 202 fewer to 54 more)	⊕⊕⊕ LOW	IMPORTANT
Clinical and endoscopic remission - 2.4g versus 4.8g												
2	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	64/172 (37.2%)	61/174 (35.1%)	RR 1.06 (0.8 to 1.40)	21 more per 1000 (from 70 fewer to 140 more)	⊕⊕⊕ LOW	IMPORTANT
Adverse events - 1.2g versus 2.4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	9/13 (69.2%)	9/14 (64.3%)	RR 1.08 (0.63 to 1.83)	51 more per 1000 (from 238 fewer to 534 more)	⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 2.4g versus 4.8g												
2	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	53/102 (52%)	48/100 (48%)	RR 1.06 (0.81 to 1.4)	29 more per 1000 (from 91 fewer to 192 more)	⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 1.2g versus 4.8g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	none	9/13 (69.2%)	10/11 (90.9%)	RR 0.76 (0.51 to 1.14)	218 fewer per 1000 (from 445 fewer to 127 more)	⊕⊕⊕ VERY LOW	IMPORTANT
Serious adverse events - 1.2g versus 2.4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/13 (7.7%)	0/14 (0%)	OR <sup>6</sup> 7.98 (0.16 to 403.24)	80 more per 1000 (from 110 fewer to 260 more) <sup>7</sup>	⊕⊕⊕ VERY LOW	IMPORTANT
Serious adverse events - 2.4g versus 4.8g												
2	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/172 (1.7%)	2/174 (1.1%)	OR <sup>6</sup> 1.52 (0.26 to 8.87)	10 more per 1000 (from 20 fewer to 30 more) <sup>7</sup>	⊕⊕⊕ VERY LOW	IMPORTANT
Serious adverse events - 1.2g versus 4.8g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/13 (7.7%)	0/11 (0%)	OR <sup>6</sup> 6.34 (0.12 to 323.68)	80 more per 1000 (from 120 fewer to 270 more) <sup>7</sup>	⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias, unclear blinding and a high attrition rate.

<sup>2</sup> Crosses both 0.75 and 1.25 relative risk (RR) MIDs.

<sup>3</sup> Crosses 1.25 relative risk (RR) MID.

<sup>4</sup> Limitations comprised of unclear blinding and high attrition rates.

<sup>5</sup> Crosses 0.75 relative risk (RR) MID.

<sup>6</sup> Peto odds ratio

<sup>7</sup> Risk difference.

**Table 35: Mesalamine/Mesalazine (Asacol)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Asacol) lower dose	Mesalazine (Asacol) higher dose	Relative (95% CI)	Absolute		
Clinical remission 1.6g versus 4.8g - >4≤6 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	1/11 (9.1%)	9/38 (23.7%)	RR 0.38 (0.05 to 2.71)	147 fewer per 1000 (from 225 fewer to 405 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission 2.4g versus 3.6g - 0≤2 weeks												
1	randomised trials	very serious <sup>1,2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	3/24 (12.5%)	7/24 (29.2%)	RR 0.43 (0.13 to 1.46)	166 fewer per 1000 (from 254 fewer to 134 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission 2.4g versus 3.6g - >2≤4 weeks												
1	randomised trials	very serious <sup>1,2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	9/24 (37.5%)	11/24 (45.8%)	RR 0.82 (0.42 to 1.61)	82 fewer per 1000 (from 266 fewer to 280 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 2.4g versus 3.6g ->6≤8 weeks												
1	randomised trials	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	20/66 (30.3%)	29/64 (45.3%)	RR 0.67 (0.42 to 1.05)	150 fewer per 1000 (from 263 fewer to 23 more)	⊕⊕○○ LOW	CRITICAL
Clinical remission - 2.4g versus 4.8g >2≤4 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	65/359 (18.1%)	91/365 (24.9%)	RR 0.73 (0.55 to 0.96)	67 fewer per 1000 (from 10 fewer to 112 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Clinical remission - 2.4g versus 4.8g - >4≤6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	121/347 (34.9%)	152/353 (43.1%)	RR 0.81 (0.67 to 0.98)	82 fewer per 1000 (from 9 fewer to 142 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Clinical improvement 1.6g versus 4.8g - >4≤6 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	3/11 (27.3%)	28/38 (73.7%)	RR 0.37 (0.14 to 0.99)	464 fewer per 1000 (from 7 fewer to 634 fewer)	⊕⊕○○ LOW	CRITICAL
Clinical improvement 2.4g versus 3.6g - 0≤2 weeks												
1	randomised trials	very serious <sup>1,2</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	11/24 (45.8%)	18/24 (75%)	RR 0.61 (0.37 to 0.99)	292 fewer per 1000 (from 472 fewer to 180 more)	⊕○○○ VERY LOW	CRITICAL



									1.00)	fewer to 0 more)		
<b>Clinical improvement 2.4g versus 3.6g - &gt;2≤4 weeks</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	14/24 (58.3%)	19/24 (79.2%)	RR 0.74 (0.50 to 1.09)	206 fewer per 1000 (from 396 fewer to 71 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical improvement - 2.4g versus 3.6g - &gt;6≤8 weeks</b>												
1	randomised trials	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	30/66 (45.5%)	41/64 (64.1%)	RR 0.71 (0.51 to 0.98)	186 fewer per 1000 (from 13 fewer to 314 fewer)	⊕⊕○○ LOW	CRITICAL
<b>Clinical improvement - 2.4g versus 4.8g -&gt;2≤4 weeks</b>												
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/280 (46.4%)	129/261 (49.4%)	RR 0.94 (0.79 to 1.12)	30 fewer per 1000 (from 104 fewer to 59 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Clinical improvement - 2.4g versus 4.8g -&gt;4≤6 weeks</b>												
4	randomised trials	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	426/715 (59.6%)	457/707 (64.6%)	RR 0.92 (0.85 to 1)	52 fewer per 1000 (from 97 fewer to 0 more)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Quality of Life - 2.4g versus 4.8g (Better indicated by lower values)</b>												
2	randomised trials	serious <sup>1</sup>	serious <sup>6</sup>	no serious indirectness	no serious imprecision	none	349	338	-	MD 3.31 lower (8.56 lower to 1.95 higher)	⊕⊕○○ LOW	CRITICAL
<b>Clinical and endoscopic remission - 2.4g versus 4.8g</b>												
3	randomised trials	serious <sup>5</sup>	serious <sup>6</sup>	no serious indirectness	very serious <sup>3</sup>	none	72/663 (10.9%)	70/649 (10.8%)	RR 0.97 (0.72 to 1.31)	3 fewer per 1000 (from 30 fewer to 33 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical and endoscopic remission - 2.4g versus 4.8g random effects</b>												
3	randomised trials	serious <sup>5</sup>	serious <sup>6</sup>	no serious indirectness	very serious <sup>3</sup>	none	72/663 (10.9%)	70/649 (10.8%)	RR 1.01(0.63 to 1.61)	1 more per 1000 (from 40 fewer to 66 more)	⊕○○○ VERY LOW	CRITICAL
<b>Adverse events - 2.4g versus 3.6g</b>												
1	randomised trials	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/66 (84.8%)	53/64 (82.8%)	RR 1.02 (0.88 to 1.19)	17 more per 1000 (from 99 fewer to 157 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Adverse events - 2.4g versus 4.8g</b>												
3	randomised trials	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	188/676 (27.8%)	185/665 (27.8%)	RR 0.99 (0.83 to 1.17)	3 fewer per 1000 (from 47 fewer to 47 more)	⊕⊕⊕○ MODERATE	IMPORTANT
<b>Serious adverse events - 2.4g versus 3.6g</b>												
1	randomised trials	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	2/66 (3%)	2/64 (3.1%)	RR 0.97 (0.14 to 6.68)	1 fewer per 1000 (from 27 fewer to 177 more)	⊕○○○ VERY LOW	IMPORTANT

Serious adverse events - 2.4g versus 4.8g												
3	randomised trials	serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	11/676 (1.6%)	6/665 (0.9%)	RR 1.81 (0.67 to 4.87)	7 more per 1000 (from 3 fewer to 35 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias.

<sup>2</sup> Limitations comprised of a high attrition rate.

<sup>3</sup> Crosses 0.75 and 1.25 relative risk (RR)MIDs.

<sup>4</sup> Crosses 0.75 relative risk (RR)MID.

<sup>5</sup> Limitations comprised of selection bias and unclear blinding.

<sup>6</sup>  $I^2 > 50\%$  but  $< 75\%$ .

### Subgroup analysis

A high heterogeneity value was found (64%) for the mesalazine versus mesalazine (Asacol) dose comparison on quality of life. The only difference between the two trials is the ASCENDII trial only included people with moderate disease. See Table 36 for the study differences.

**Table 36: Mesalazine versus mesalazine (Asacol) dose comparison on quality of life**

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
IRVINE2008 ASCENDI	oral mesalazine 4.8g/day vs oral mesalazine 2.4g/day (Asacol)	Mild/moderate	proctitis to pancolitis	adults
IRVINE2008ASCENDII	oral mesalazine 4.8g/day vs oral mesalazine 2.4g/day (Asacol)	moderate	proctitis to pancolitis	adults

There was also a high heterogeneity value (54%) for clinical and endoscopic remission for 2.4g versus 4.8g of Asacol. When the studies were split by severity of disease, the heterogeneity still remained (66%). The SANDBORN2009A study appears to favour the use of a lower dose compared to the other two studies. When the studies were split by extent of disease (all extents, no proctitis) the heterogeneity was removed. However, it was felt that extent of disease would not explain the differences in efficacy seen between the studies, with a non proctitis population favouring the lower Asacol dose. The explanation for the difference seen is unclear. See Table 37 for study differences.

**Table 37: Clinical and endoscopic remission for 2.4g versus 4.8g Asacol**

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
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Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
HANAUER2005 (moderate) ASCEND II	oral mesalazine 4.8g/day vs oral mesalazine 2.4g/day (Asacol tablets)	Moderate	All types. Around 50% left sided or extensive disease. ~15% proctitis.	18-75 years
HANAUER2007 ASCEND I	oral mesalazine 4.8g/day vs oral mesalazine 2.4g/day (Asacol tablets)	Mild/ moderate	All types. Around 50% left sided or extensive disease. ~18% proctitis.	18-75 years
SANDBORN2009A ASCEND III	oral mesalazine 4.8g/day vs oral mesalazine 2.4g/day (Asacol tablets)	Moderate	Not proctitis. Around 50% left sided or extensive disease.	18-75 years

**Table 38: Mesalazine (Salofalk)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Salofalk) lower dose	Mesalazine (Salofalk) higher dose	Relative (95% CI)	Absolute		
Clinical remission - 1.5g versus 3.0g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	52/103 (50.5%)	71/107 (66.4%)	RR 0.76 (0.6 to 0.96)	159 fewer per 1000 (from 27 fewer to 265 fewer)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 3.0g versus 4.5g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	71/107 (66.4%)	58/106 (54.7%)	RR 1.21 (0.97 to 1.51)	115 more per 1000 (from 16 fewer to 279 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 1.5g versus 4.5g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	52/103 (50.5%)	58/106 (54.7%)	RR 0.92 (0.71 to 1.19)	44 fewer per 1000 (from 159 fewer to 104 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 1.5g versus 3.0g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	66/103 (64.1%)	80/107 (74.8%)	RR 0.86 (0.71 to 1.03)	105 fewer per 1000 (from 217 fewer to 22 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 3.0g versus 4.5g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	80/107 (74.8%)	70/106 (66%)	RR 1.13 (0.95 to 1.35)	86 more per 1000 (from 33 fewer to 231 more)	⊕○○○ VERY	CRITICAL

											LOW	
<b>Clinical improvement - 1.5g versus 4.5g</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/103 (64.1%)	70/106 (66%)	RR 0.97 (0.8 to 1.18)	20 fewer per 1000 (from 132 fewer to 119 more)	⊕⊕⊕ LOW	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Adverse events - 1.5g versus 3.0g</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	64/102 (62.7%)	66/108 (61.1%)	RR 1.03 (0.83 to 1.27)	18 more per 1000 (from 104 fewer to 165 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Adverse events - 3.0g versus 4.5g</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	66/108 (61.1%)	63/108 (58.3%)	RR 1.05 (0.84 to 1.3)	29 more per 1000 (from 93 fewer to 175 more)	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Adverse events - 1.5g versus 4.5g</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	64/102 (62.7%)	63/108 (58.3%)	RR 1.08 (0.86 to 1.34)	47 more per 1000 (from 82 fewer to 198 more)	⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias, unclear blinding and high attrition rates.

<sup>2</sup> Crosses 0.75 relative risk (RR) MID.

<sup>3</sup> Crosses 1.25 relative risk (RR) MID.

**Table 39: Olsalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olsalazine lower dose	Olsalazine higher dose	Relative (95% CI)	Absolute		
Clinical remission - 2g versus 3g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	11/92 (12%)	16/91 (17.6%)	RR 0.68 (0.33 to 1.38)	56 fewer per 1000 (from 118 fewer to 67 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 1.5g versus 3g												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	serious <sup>4</sup>	very serious <sup>2</sup>	none	4/15 (26.7%)	7/14 (50%)	RR 0.53 (0.2 to 1.43)	235 fewer per 1000 (from 400 fewer to 215 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - 2g versus 3g												

1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>5</sup>	none	32/92 (34.8%)	41/91 (45.1%)	RR 0.77 (0.54 to 1.11)	104 fewer per 1000 (from 207 fewer to 50 more)	⊕○○○ VERY LOW	IMPORTANT
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<sup>1</sup> Limitations comprised of selection bias and a high attrition rate.

<sup>2</sup> Crosses the 0.75 and 1.25 relative risk (RR) MIDs.

<sup>3</sup> Limitations comprised of selection bias.

<sup>4</sup> Includes <10% people with severe disease.

<sup>5</sup> Crosses the 0.75 relative risk (RR) MID.

### 5.16.3 Oral aminosalicylates versus oral aminosalicylates (mesalazine comparison)

**Table 40: Eudragit S (Asacol 2.4g) versus Ethylcellulose (Pentasa 2.25g)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pentasa	Asacol	Relative (95% CI)	Absolute		
Clinical remission												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	20/66 (30.3%)	18/63 (28.6%)	RR 1.06 (0.62 to 1.81)	17 more per 1000 (from 109 fewer to 231 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	30/66 (45.5%)	31/63 (49.2%)	RR 0.92 (0.64 to 1.33)	39 fewer per 1000 (from 177 fewer to 162 more)	⊕○○○ VERY LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/66 (84.8%)	55/63 (87.3%)	RR 0.97 (0.85 to 1.12)	26 fewer per 1000 (from 131 fewer to 105 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Serious adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	2/66 (3%)	3/63 (4.8%)	RR 0.64 (0.11 to 3.68)	17 fewer per 1000 (from 42 fewer to 128 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of high attrition rates.

<sup>2</sup> Crosses the 0.75 and 1.25 relative risk (RR) MIDs.

**Table 41: Eudragit L coated versus Ethylcellulose coated**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Eudragit L)	Mesalazine (Ethylcellulose)	Relative (95% CI)	Absolute		

<b>Clinical remission</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/131 (63.4%)	81/127 (63.8%)	RR 0.99 (0.83 to 1.19)	6 fewer per 1000 (from 108 fewer to 121 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Clinical improvement</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/109 (79.8%)	82/106 (77.4%)	RR 1.03 (0.9 to 1.19)	23 more per 1000 (from 77 fewer to 147 more)	⊕⊕⊕O MODERATE	CRITICAL
<b>Quality of Life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	46/109 (42.2%)	46/106 (43.4%)	RR 0.97 (0.71 to 1.32)	13 fewer per 1000 (from 126 fewer to 139 more)	⊕OOO VERY LOW	CRITICAL
<b>Adverse events</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	74/131 (56.5%)	66/127 (52%)	RR 1.09 (0.87 to 1.36)	47 more per 1000 (from 68 fewer to 187 more)	⊕⊕OO LOW	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	4/131 (3.1%)	2/127 (1.6%)	RR 1.94 (0.36 to 10.4)	15 more per 1000 (from 10 fewer to 148 more)	⊕OOO VERY LOW	IMPORTANT
<b>Hospitalisations</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	4/131 (3.1%)	2/127 (1.6%)	RR 1.94 (0.36 to 10.4)	15 more per 1000 (from 10 fewer to 148 more)	⊕OOO VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of baseline differences and unclear blinding.

<sup>2</sup> Crosses the 0.75 and 1.25 relative risk (RR)MIDs.

<sup>3</sup> Crosses the 1.25 relative risk (RR) MID.

**Table 42: Eudragit S (Ipocol) versus Eudragit S (Asacol)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Ipocol)	Mesalazine (Asacol)	Relative (95% CI)	Absolute		
Clinical remission												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	12/46 (26.1%)	12/42 (28.6%)	RR 0.91 (0.46 to 1.81)	26 fewer per 1000 (from 154 fewer to 231 more)	⊕○○○ VERY LOW	CRITICAL
Quality of Life												

0	No evidence available					none	-	-	-	-		CRITICAL
<b>Adverse events</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	34/46 (73.9%)	31/42 (73.8%)	RR 1 (0.78 to 1.28)	0 fewer per 1000 (from 162 fewer to 207 more)	⊕⊕⊕ LOW	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/46 (0%)	2/42 (4.8%)	OR <sup>4</sup> 0.12 (0.01 to 1.96)	42 fewer per 1000 (from 47 fewer to 42 more) <sup>5</sup>	⊕⊕⊕ VERY LOW	IMPORTANT
<b>Colectomy</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/46 (0%)	1/42 (2.4%)	OR <sup>4</sup> 0.12 (0 to 6.23)	21 fewer per 1000 (from 24 fewer to 108 more) <sup>5</sup>	⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of unclear blinding and a high attrition rate.

<sup>2</sup> Crosses the 0.75 and 1.25 relative risk (RR) MIDs.

<sup>3</sup> Crosses the 1.25 relative risk (RR) MID.

<sup>4</sup> Crosses the 1.25 relative risk (RR) MID.

<sup>5</sup> Risk difference.

**Table 43: Mesalazine (Mezavant XL) versus mesalazine (Asacol)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Mezavant XL)	Mesalazine (Asacol)	Relative (95% CI)	Absolute		
Clinical remission												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	35/84 (41.7%)	29/86 (33.7%)	RR 1.24 (0.84 to 1.82)	81 more per 1000 (from 54 fewer to 277 more)	⊕⊕⊕ LOW	CRITICAL
Clinical improvement												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	51/84 (60.7%)	48/86 (55.8%)	RR 1.09 (0.84 to 1.4)	50 more per 1000 (from 89 fewer to 223 more)	⊕⊕⊕ LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	58/84 (69%)	53/86 (61.6%)	RR 1.12 (0.9 to 1.4)	74 more per 1000 (from 62 fewer to 247 more)	⊕⊕⊕ LOW	IMPORTANT
Clinical and endoscopic remission												

1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	34/84 (40.5%)	28/86 (32.6%)	RR 1.24 (0.83 to 1.85)	78 more per 1000 (from 55 fewer to 277 more)	⊕⊕⊕ LOW	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	1/84 (1.2%)	2/86 (2.3%)	RR 0.51 (0.05 to 5.54)	11 fewer per 1000 (from 22 fewer to 106 more)	⊕⊕⊕ VERY LOW	IMPORTANT

1 Limitations comprised of unclear blinding and a high attrition rate.

2 Crosses the 1.25 relative risk (RR) MID.

3 Crosses the 0.75 and 1.25 relative risk (RR)t MIDs.

#### 5.16.4 Oral aminosalicylates versus oral aminosalicylates (aminosalicylates comparison)

**Table 44: Olsalazine versus sulphasalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olsalazine	Sulphasalazine	Relative (95% CI)	Absolute		
Clinical remission - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	4/28 (14.3%)	6/28 (21.4%)	RR 0.67 (0.21 to 2.11)	71 fewer per 1000 (from 169 fewer to 238 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >6≤8 weeks												
2	randomised trials	very serious <sup>3</sup>	serious <sup>4</sup>	serious <sup>5</sup>	very serious <sup>6</sup>	none	20/49 (40.8%)	18/49 (36.7%)	RR 1.11 (0.69 to 1.78)	40 more per 1000 (from 114 fewer to 287 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >8 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	4/28 (14.3%)	9/28 (32.1%)	RR 0.44 (0.15 to 1.28)	180 fewer per 1000 (from 273 fewer to 90 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >6≤8 weeks												
1	randomised trials	very serious <sup>7</sup>	no serious inconsistency	serious <sup>5</sup>	serious <sup>8</sup>	none	20/21 (95.2%)	15/21 (71.4%)	RR 1.33 (1 to 1.78)	236 more per 1000 (from 0 more to 557 more)	⊕○○○ VERY LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >6≤8 weeks												
2	randomised trials	very serious <sup>3</sup>	serious <sup>4</sup>	serious <sup>5</sup>	very serious <sup>2</sup>	none	16/38 (42.1%)	18/45 (40%)	RR 1.05 (0.61 to 1.8)	20 more per 1000 (from 156 fewer to 320 more)	⊕○○○ VERY	IMPORTANT



											LOW	
Clinical and endoscopic remission - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >6≤8 weeks												
2	randomised trials	very serious <sup>3</sup>	serious <sup>4</sup>	serious <sup>5</sup>	serious <sup>8</sup>	none	18/38 (47.4%)	13/45 (28.9%)	RR 1.47 (0.89 to 2.43)	136 more per 1000 (from 32 fewer to 413 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission - 3g olsalazine versus 6g SASP (equivalent of 2.7g 5-ASA versus 2.3g 5-ASA) - >4≤6 weeks												
1	randomised trials	serious <sup>9</sup>	no serious inconsistency	serious <sup>10</sup>	very serious <sup>6</sup>	none	6/27 (22.2%)	9/28 (32.1%)	RR 0.69 (0.28 to 1.68)	100 fewer per 1000 (from 231 fewer to 219 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission - 3g olsalazine versus 6g SASP (equivalent of 2.7g 5-ASA versus 2.3g 5-ASA) ->8 weeks												
1	randomised trials	serious <sup>9</sup>	no serious inconsistency	serious <sup>10</sup>	very serious <sup>6</sup>	none	14/26 (53.8%)	11/27 (40.7%)	RR 1.32 (0.74 to 2.35)	130 more per 1000 (from 106 fewer to 550 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events - 2g olsalazine versus 4g SASP (equivalent of 1.8g 5-ASA versus 1.5g 5-ASA) - >8 weeks												
1	randomised trials	serious <sup>11</sup>	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	none	11/28 (39.3%)	13/28 (46.4%)	RR 0.85 (0.46 to 1.56)	70 fewer per 1000 (from 251 fewer to 260 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection and measurement bias.

<sup>2</sup> Crosses the 0.75 and 1.25 relative risk (RR) MIDs.

<sup>3</sup> Limitations comprised of selection and measurement bias and unclear blinding.

<sup>4</sup>  $I^2 > 50\%$  and  $< 75\%$ .

<sup>5</sup> Includes people with severe disease.

<sup>6</sup> Crosses the 0.75 and 1.25 relative risk (RR) MIDs.

<sup>7</sup> Limitations comprised of selection bias, unclear blinding and baseline data.

<sup>8</sup> Crosses the 1.25 relative risk (RR) MID.

<sup>9</sup> Limitations comprised of unclear baseline characteristics and a high attrition rate.

<sup>10</sup> May include people with severe disease.

<sup>11</sup> Limitations include selection bias.

### Subgroup analysis

There was high heterogeneity for the olsalazine (2g) and SASP (4g) comparison in clinical remission at  $>6\leq 8$  weeks (61%) and endoscopic remission at 8 weeks (59%). There were several differences between the studies that could account for the inconsistency, FERRY1993<sup>66</sup> was a paediatric study, had only a mild to moderate population and was set in North America compared to JIANG2004<sup>104</sup> which was an adult study, included a small percentage of severe patients and was set in China. See Table 45 for the study differences.

**Table 45: Olsalazine (2g) versus SASP (4g)**

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
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Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
FERRY1993 North America	Maximum 2g olsalazine vs maximum 4g SASP	Mild/moderate	Localised proctitis excluded	2-17 years
JIANG2004 China	2g olsalazine vs 4g SASP	10% (n=2) of the olsalazine group had severe disease 5% (n=1) of the SASP group had severe disease	No inclusion criteria	adults

**Table 46: Balsalazide versus mesalazine (all types)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Balsalazide	Mesalazine	Relative (95% CI)	Absolute		
Clinical remission - 6.75g balsalazide (equivalent to 2.4g 5-ASA) versus 2.4g mesalazine - 0≤2 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	32/50 (64%)	21/49 (42.9%)	RR 1.49 (1.02 to 2.19)	210 more per 1000 (from 9 more to 510 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - 6.75g balsalazide (equivalent to 2.4g 5-ASA) versus 2.4g mesalazine - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	35/50 (70%)	25/49 (51%)	RR 1.37 (0.99 to 1.91)	189 more per 1000 (from 5 fewer to 464 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical remission - 6.75g balsalazide (equivalent to 2.4g 5-ASA) versus 2.4g mesalazine ->6≤8 weeks												
2	randomised trials	very serious <sup>1</sup>	very serious <sup>4</sup>	serious <sup>2</sup>	serious <sup>3</sup>	none	77/123 (62.6%)	60/126 (47.6%)	RR 1.31 (1.04 to 1.65)	148 more per 1000 (from 19 more to 310 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical remission - 6.75g balsalazide (equivalent to 2.4g 5-ASA) versus 2.4g mesalazine - >8 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	44/50 (88%)	28/49 (57.1%)	RR 1.54 (1.18 to 2)	309 more per 1000 (from 103 more to 571 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA - >6≤8 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>5</sup>	serious <sup>3</sup>	none	22/34 (64.7%)	22/38 (57.9%)	RR 1.12 (0.77 to 1.61)	69 more per 1000 (from 133 fewer to 353 more)	⊕○○○ VERY LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL

Clinical and endoscopic remission - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA - >2≤4 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	19/50 (38%)	6/49 (12.2%)	RR 3.1 (1.35 to 7.11)	257 more per 1000 (from 43 more to 748 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA - >6≤8 weeks, fixed effects												
3	randomised trials	very serious <sup>1</sup>	serious <sup>6</sup>	very serious <sup>5</sup>	serious <sup>3</sup>	none	74/169 (43.8%)	54/174 (31%)	RR 1.42 (1.07 to 1.87)	130 more per 1000 (from 22 more to 270 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA - >6≤8 weeks, random effects												
3	randomised trials	very serious <sup>1</sup>	serious <sup>6</sup>	very serious <sup>5</sup>	serious <sup>3</sup>	none	74/169 (43.8%)	54/174 (31%)	RR 1.47 (0.88 to 2.46)	146 more per 1000 (from 37 fewer to 453 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA - >8 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	serious <sup>5</sup>	serious <sup>3</sup>	none	31/50 (62%)	18/49 (36.7%)	RR 1.69 (1.1 to 2.59)	253 more per 1000 (from 37 more to 584 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA												
3	randomised trials	very serious <sup>1</sup>	no serious inconsistency	very serious <sup>4</sup>	serious <sup>7</sup>	none	92/187 (49.2%)	118/189 (62.4%)	RR 0.79 (0.66 to 0.95)	131 fewer per 1000 (from 31 fewer to 212 fewer)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events - 6.75g balsalazide (equivalent of 2.34g 5-ASA) versus 2.4g 5-ASA												
3	randomised trials	very serious <sup>1</sup>	no serious inconsistency	very serious <sup>5</sup>	serious <sup>7</sup>	none	1/187 (0.53%)	8/189 (4.2%)	RR 0.22 (0.05 to 1.01)	33 fewer per 1000 (from 40 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias and a high attrition rate.

<sup>2</sup> Likely to include people with severe disease.

<sup>3</sup> Crosses the 1.25 relative risk (RR) MID.

<sup>4</sup>  $I^2 > 75\%$ .

<sup>5</sup> Includes people with severe disease.

<sup>6</sup>  $I^2 > 50\%$  and  $< 75\%$ .

<sup>7</sup> Crosses the 0.75 relative risk (RR) MID.

### Subgroup analysis

There was very high heterogeneity (77%) in the Balsalazide and mesalazine (2.4g) comparison in clinical remission at 8 weeks. There are differences in severity, GREEN1998<sup>76</sup> had people with severe disease and PRUITT 2002<sup>172</sup> included some paediatric patients. See Table 47 for study differences.

**Table 47: Balsalazide versus mesalazine (2.4g) clinical remission**

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
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Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
GREEN1998	Balsalazide 6.75g vs mesalazine 2.4g- (Eudragit-S)	Moderate or severe (but this was based on the patient's overall evaluation of symptoms not Truelove & Witts <sup>w</sup> ) and grade 2-4 on sigmoidoscopy	Extent: ≥12cm beyond the anal margin	Adults
PRUITT2002	Balsalazide 6.75g vs mesalazine 2.4g (Asacol)	Mild/moderate	Extent: at least 12cm of sigmoidoscopically verified disease	12-80 years

There was high heterogeneity (59%) in the Balsalazide and mesalazine (2.4g) comparison in clinical and endoscopic remission at 8 weeks. When GREEN1998<sup>76</sup> is removed the heterogeneity disappears. This could be explained by the severe patients in the GREEN1998<sup>76</sup> population and reduced efficacy of the lower dose of mesalazine in this group. See Table 48 for the study differences.

**Table 48: Balsalazide versus mesalazine (2.4g) clinical and endoscopic remission**

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
GREEN1998	Balsalazide 6.75g vs mesalazine 2.4g- (Eudragit-S)	Moderate or severe (but this was based on the patient's overall evaluation of symptoms not Truelove & Witts <sup>x</sup> ) and grade 2-4 on sigmoidoscopy	Extent: ≥12cm beyond the anal margin	Adults
PRUITT2002	Balsalazide 6.75g vs mesalazine 2.4g (Asacol)	Mild/moderate	Extent: at least 12cm of sigmoidoscopically verified disease	12-80 years

<sup>w</sup> No symptoms (excluded at entry), mild (aware of symptoms, easily tolerated, no interference with normal activities. They were also excluded at entry), moderate (occasional interference with normal activities), severe (frequent interference with normal activities).

<sup>x</sup> No symptoms (excluded at entry), mild (aware of symptoms, easily tolerated, no interference with normal activities. They were also excluded at entry), moderate (occasional interference with normal activities), severe (frequent interference with normal activities).

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
LEVINE2002	Balsalazide 6.75g vs mesalazine 2.4g (Asacol	Mild/moderate	No extent restriction	18-80 years

**Table 49: Regimen comparison**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower number of times per day	Higher number of times per day	Relative (95% CI)	Absolute		
Clinical remission - Once versus three times per day												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	151/191 (79.1%)	143/189 (75.7%)	RR 1.04 (0.94 to 1.17)	30 more per 1000 (from 45 fewer to 129 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical remission - Twice a day versus four times a day												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	29/74 (39.2%)	28/76 (36.8%)	RR 1.06 (0.71 to 1.6)	22 more per 1000 (from 107 fewer to 221 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - Twice a day versus four times a day												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/74 (78.4%)	58/76 (76.3%)	RR 1.03 (0.86 to 1.22)	23 more per 1000 (from 107 fewer to 168 more)	⊕⊕○○ LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - Once versus three times per day												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	135/191 (70.7%)	132/189 (69.8%)	RR 1.01 (0.89 to 1.15)	7 more per 1000 (from 77 fewer to 105 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse events - Once versus three times per day												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	55/191 (28.8%)	61/189 (32.3%)	RR 0.89 (0.66 to 1.21)	36 fewer per 1000 (from 110 fewer to 68 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Serious adverse events - Once versus three times per day												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	4/191 (2.1%)	2/189 (1.1%)	RR 1.98 (0.37 to 10.68)	10 more per 1000 (from 7 fewer to 102 more)	⊕⊕○○ LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias, no blinding and a high attrition rate.

<sup>2</sup> Crosses the 0.75 and 1.25 relative risk (RR)MIDs.

<sup>3</sup> Crosses the 0.75 relative risk (RR) MID.

**Table 50: Preparation comparison**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA granules	Oral ASA tablets	Relative (95% CI)	Absolute		
Clinical remission - >2≤4weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	54/114 (47.4%)	48/115 (41.7%)	RR 1.13 (0.85 to 1.52)	54 more per 1000 (from 63 fewer to 217 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >6≤8 weeks												
3	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	224/369 (60.7%)	214/370 (57.8%)	RR 1.05 (0.93 to 1.18)	29 more per 1000 (from 40 fewer to 104 more)	⊕⊕○○ LOW	CRITICAL
Clinical improvement												
1	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	58/76 (76.3%)	52/77 (67.5%)	RR 1.13 (0.93 to 1.38)	88 more per 1000 (from 47 fewer to 257 more)	⊕○○○ VERY LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	67/179 (37.4%)	71/178 (39.9%)	RR 0.94 (0.72 to 1.22)	24 fewer per 1000 (from 112 fewer to 88 more)	⊕○○○ VERY LOW	IMPORTANT
Clinical and endoscopic remission												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	61/179 (34.1%)	59/178 (33.1%)	RR 1.03 (0.77 to 1.38)	10 more per 1000 (from 76 fewer to 126 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events, random effects												
2	randomised trials	very serious <sup>1</sup>	serious <sup>5</sup>	no serious indirectness	very serious <sup>6</sup>	none	92/295 (31.2%)	85/299 (28.4%)	RR 1.08 (0.74 to 1.57)	23 more per 1000 (from 74 fewer to 162 more)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events												
2	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>6</sup>	none	3/295 (1%)	8/299 (2.7%)	RR 0.41 (0.12 to 1.43)	16 fewer per 1000 (from 24 fewer to 12 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of selection bias and unclear attrition rate.

<sup>2</sup> Crosses the 1.25 relative risk (RR) MID.

<sup>3</sup> Limitations comprised of selection bias, a high attrition rate and no blinding.

<sup>4</sup> Crosses the 0.75 relative risk (RR) MID.

<sup>5</sup>  $I^2 > 50\% < 75\%$ .

<sup>6</sup> Crosses both the 0.75 and 1.25 relative risk (RR) MIDs.

### Subgroup analysis

There was high heterogeneity (56%) between the tablet and granule comparison in adverse events. The studies show opposite effects investigation of the subgroups does not explain the heterogeneity. See Table 51 for the study differences.

**Table 51: Tablet versus granules**

Study	Drug (mechanism of release) & dose	Severity of disease	Extent of disease	Age
MARAKHOUSKI2005	3g mesalazine pellets (Salofalk) vs 3g mesalazine tablets	Severity: Mild to moderately active UC (CAI score of 6-12) and an EI score of $\geq 4$	Extent: $\geq 15$ cm beyond the anal margin	18-70 years
RAEDLER2004	3g mesalazine pellets (Salofalk) vs 3g mesalazine tablets	Severity: Recurrent mild to moderate UC (CAI1-4 of $\geq 4$ and an EI $\geq 4$ ) Diagnosed by clinical appearance, colonoscopy and histology	Extent: $\geq 12$ cm proximally	18-75 years

## 5.17 Economic evidence

### Published literature

Three studies were included with the relevant comparison.<sup>25, 26, 132</sup> These are summarised in the economic evidence profile below. See also the study selection flow chart in Appendix E and study evidence tables in Appendix G.

One study<sup>171</sup> that met the inclusion criteria was selectively excluded due to the availability of a similar study with greater applicability. See Appendix F for list of excluded studies, with reasons for exclusion given.



**Table 52: Economic evidence profile: oral aminosalicylates**

Study	Limitations	Applicability	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
<b>2.4g/day Mesalazine (Mezavant XL) versus 2.4g/day Mesalazine (Asacol)</b>							
Brereton <sup>25</sup>	Potentially serious limitations <sup>(a)</sup>	Directly applicable	Patients received an increased dose of mesalazine (2.4g to 4.8g) if they failed to respond to 1 <sup>st</sup> line mesalazine treatment. The effect of adherence to maintenance therapy was captured.	£8	0.011 QALYs	£749 per QALY gained	Probabilistic sensitivity analysis showed that Mezavant XL mesalazine dominated mesalazine on 62% of the occasions and the probability of being cost-effective at a threshold of £20,000 was 74%.
<b>High dose (4.8g/day) versus standard dose (2.4g/day) Mesalazine (Asacol)</b>							
Buckland <sup>26</sup>	Minor limitations	Directly applicable	Relative treatment effect was obtained from two studies.	-£92	0.0016 QALYs	High dose dominates (less costly and more effective)	The results were sensitive to the duration of 1 <sup>st</sup> line mesalazine treatment.  The probability of HD mesalazine being cost-effective at a threshold of £30,000/QALY was 72%.
<b>6.75g/day Balsalazide versus 2.4g-4.8g/day Mesalazine delayed tablets</b>							
Mackowiak <sup>132</sup>	Potentially serious limitations <sup>(b)</sup>	Partially applicable <sup>(c)</sup>	Relative treatment effect was obtained from one study.	-£1,104 <sup>(d)</sup>	26 more days without symptoms or steroids	Balsalazide dominates (less total costs per symptom or steroid free day)	The sensitivity analysis methods not clearly defined however balsalazide is reported to be the cost-effective option.

(a) A 5 year time horizon was modelled in the base case analysis; consequently, relapse and maintenance therapy were included.

(b) Cost sources not clearly reported and unclear methodology regarding sensitivity analysis.

(c) The cost-effectiveness model was designed to reflect the management of ulcerative colitis in the US therefore resource use may not be applicable to the UK health system. The value of health effects were not expressed in terms of quality-adjusted life years.

(d) Costs were converted from US dollars to UK pounds using Purchasing Power Parities<sup>161</sup>

### **New cost-effectiveness analysis**

These studies help to highlight the cost-effectiveness of specific aminosalicylates (ASAs) or ASA doses. However, other ASAs are available which have not been addressed. In addition, the studies have modelled different treatment sequences after failure of first line treatment. This makes comparability across the studies difficult. The GDG considered that there are other clinically relevant sequences that have not been captured and hence this topic was considered to be a top priority for original economic analysis. The original economic analysis addressed the most cost-effective treatment sequence for induction of remission. The analysis is detailed in Appendix L.

## **5.18 Evidence statements**

### **5.18.1 Clinical evidence statements**

#### **5.18.1.1 Oral aminosalicylates versus placebo**

##### **Clinical remission**

Oral ASAs were more clinically effective at increasing clinical remission rates at 4-6 and 6-8 weeks compared to placebo but may not be at 2-4 and >8 weeks [low to very low quality evidence, 2 studies, N=196; 6 studies, N=1594; 2 studies, N=149; 1 study, N=273].

##### **Clinical improvement**

Very low quality evidence showed Oral ASAs increased clinical improvement rates at all time points weeks compared to placebo [very low quality evidence, 7 studies, N=405; 4 studies, N=362; 6 studies, N=1590].

##### **Important outcomes**

Very low quality evidence showed oral ASAs are more clinically effective at increasing endoscopic remission rates at  $>6 \leq 8$  weeks compared to placebo but not at  $>8$  weeks [very low quality evidence, 3 studies, N=855; 1 study, N=273]. Oral ASAs are more clinically effective at increasing clinical and endoscopic remission rates at  $>6 \leq 8$  weeks compared to placebo [4 studies, N=1097]. Very low quality evidence showed there was no clinically important difference in adverse or serious adverse events rates between oral ASAs and placebo [very low quality evidence, 9 studies, N=1527; 5 studies, N=1367].

#### **5.18.1.2 Dose comparison - Pentasa**

##### **Clinical remission**

There may be no clinically important difference in clinical remission rates between doses of mesalazine (Pentasa), [very low quality evidence, 1 study, N=171, 1 study, N=118].

##### **Clinical improvement**

Four grams of mesalazine (Pentasa) may be more clinically effective at increasing clinical improvement rates than 2g or 2.25g [very low quality evidence, 1 study, N=192, 1 study, N=118].

##### **Important outcomes**

There may be no clinically important difference in endoscopic remission rates (2g vs 4g), adverse events, serious adverse events (2g or 2.25g vs. 4g) or hospitalisations (2g vs 4g) between doses of mesalazine (Pentasa), the direction of the estimate of effect did not favour 2g or 4g [very low quality evidence, 1 study, N=192; 1 study, N=192; 1 study, N=123; 1 study, N=192; 1 study, N=123; 1 study, N=123.]

### 5.18.1.3 Dose comparison – Mezavant XL (mesalazine)

#### Clinical remission and clinical improvement

There may be no clinically important difference in clinical remission or clinical improvement rates between 2.4g and 4.8g of mesalazine (Mezavant XL) [very low to moderate quality evidence, 3 studies, N=356; 2 studies, N=359].

#### Important outcomes

There is no clinically important difference in endoscopic remission rates between 2.4g mesalazine (Mezavant XL) and 4.8g [Moderate quality evidence, 1 study, N=169] and there may be no clinically important difference in clinical and endoscopic remission rates [Low quality evidence, 2 studies, N=346]. There may be no clinically important difference in adverse or serious adverse events rates between 2.4g and 4.8g mesalazine (Mezavant XL) [very low quality evidence, 2 studies, N=215; 2 studies, N=359].

### 5.18.1.4 Dose comparison – Asacol (mesalazine)

#### Clinical remission

4.8g mesalazine (Asacol) may be more clinically effective than 1.6g at 6 weeks, 3.6g mesalazine (Asacol) may be more clinically effective than 2.4g at increasing clinical remission rates at 2 and 8 weeks but there may be no difference at 4 weeks. There may be no difference between 2.4g and 4.8g at 3 and 6 weeks [very low to moderate quality evidence, 1 study, N=49; 1 study, N=48, 1 study, N=130; 1 study, N=48; 1 study, N=724].

#### Clinical improvement

3.6g mesalazine (Asacol) may be more clinically effective at increasing clinical improvement rates compared to 2.4g at 2, 4 and 8 weeks and 4.8g of Asacol compared to 1.6g at 6 weeks but there may be no difference between 2.4g and 4.8g mesalazine (Asacol) at 3 and 6 weeks [low to moderate quality evidence, 1 study, N=48; 1 study, N=48; 1 study, N=130; 1 study, N=49; 2 studies, N=541; 3 studies, N=1422].

#### Quality of life

There is no clinically important difference in quality of life scores between 2.4g and 4.8g mesalazine (Asacol) [low quality evidence, 2 studies, N= study, N=687].

#### Important outcomes

There may be no clinical difference in clinical and endoscopic remission rates between 2.4g and 4.8g mesalazine (Asacol) [low quality evidence, 3 studies, N=1312]. There was no clinically important difference in adverse events rates between 2.4g mesalazine (Asacol) compared to 3.6g or 4.8g [moderate quality evidence, 1 study, N=130; 3 studies, N=1341]. There may be no difference in clinically important serious adverse event rates between 2.4g mesalazine (Asacol) compared to 3.6g or 4.8g [very low quality evidence, 1 study, N=130; 3 studies, N=1341].

### 5.18.1.5 Dose comparison – Salofalk (mesalazine)

#### Clinical remission

Low quality evidence showed 3g mesalazine (Salofalk) may be more clinically effective at increasing clinical remission rates compared to 1.5g and 4.5g mesalazine (Salofalk) at 8 weeks but there may be no clinical difference between 4.5g or 1.5g [very low to low quality evidence, 1 study, N=210; 1 study, N=209].

#### Clinical improvement

Very low quality evidence showed 3g mesalazine (Salofalk) may be more clinically effective at increasing clinical improvement rates compared to 1.5g but there may be no clinical difference in clinical remission rates between 3.0g and 4.5g and 1.5g and 4.5g [very low quality evidence, 1 study, N=146;N=213;N=209].

**Important outcomes**

There may be no clinical difference in adverse event rates between any of the doses of mesalazine (Salofalk) [very low quality evidence, 1 study, N=210;N=216;N=210].

**5.18.1.6 Dose comparison – Olsalazine**

**Clinical remission**

There may be no clinical difference in clinical remission rates between 2g and 3g olsalazine [very low quality evidence, 1 study, N=183].

**Clinical improvement**

3g olsalazine may be more clinically effective at increasing clinical improvement rates compared to 1.5g [very low quality evidence, 1 study, N=29].

**Important outcomes**

3g olsalazine may be more clinically effective at increasing clinical improvement rates compared to 2g [very low quality, 1 study, N=29].

**5.18.1.7 Mesalazine comparison – Eudragit S (400mg Asacol tablets, 2.4g) versus Ethylcellulose (Pentasa, 2.25g)**

**Clinical remission and clinical improvement**

There may be no clinical difference between Ethylcellulose (Pentasa) and Eudragit S (Asacol) at increasing clinical remission rates and may be no difference in clinical improvements rates between Ethylcellulose (Pentasa) and Eudragit S (Asacol) [very low quality evidence, one study, N=129].

**Important outcomes**

There was no clinical difference in adverse or serious adverse event rates between Ethylcellulose (Pentasa) and Eudragit S (Asacol) [very low to moderate evidence quality evidence 1 study, N=129].

**5.18.1.8 Mesalazine comparison – Eudragit L versus Ethylcellulose**

**Clinical remission**

Moderate quality evidence showed there was no clinical difference between Ethylcellulose and Eudragit L coated mesalazine at increasing clinical remission rates or clinical improvement rate [moderate quality evidence, 1 study, N=158; 1 study, N=215].

**Important outcomes**

There may be no clinical difference between Ethylcellulose and Eudragit L coated mesalazine at increasing endoscopic remission rates, adverse or serious adverse events or hospitalisations [very low quality evidence, 1 study, N=215; 1 study, N=158; 1 study, N=158; 1 study, N=158].

**5.18.1.9 Mesalazine comparison – Eudragit S (Ipocol) versus Eudragit S (Asacol)**

**Clinical remission**

There may be no clinical difference between Eudragit S coated (Ipocol) and Eudragit S coated (Asacol) mesalazine at increasing clinical remission rates [very low quality, 1 study, N=88].

**Important outcomes**

There may be no clinical difference between Eudragit S coated (Ipocol) and Eudragit S coated (Asacol) mesalazine in adverse or serious adverse events rates or colectomy rates [low to very low quality evidence, 1 study, N=88; 1 study, N=88; 1 study, N=88].

**5.18.1.10 Mesalazine comparison – Mezavant XL and Asacol**

**Clinical remission and clinical improvement**

There may be no clinical difference in increasing clinical remission or clinical improvement rates between 2.4g mesalazine (Mezavant XL) and 2.4g mesalazine (Asacol) at 8 weeks [low quality evidence, 1 study, N=161; 1 study, N=161].

**Important outcomes**

Low quality evidence showed there may be no clinical difference in increasing endoscopic, clinical and endoscopic remission or serious adverse event rates between 2.4g mesalazine (Mezavant XL) and 2.4g mesalazine (Asacol) at 8 weeks [low quality evidence, 1 study, N=161; 1 study, N=161; 1 study, N=163].

**5.18.1.11 Interclass comparison – Olsalazine versus sulphasalazine**

**Clinical remission**

There may be no clinical difference between 2g olsalazine and 4g sulphasalazine at 2-4 and 6-8 weeks in increasing clinical remission rates [very low quality evidence, 1 study, N=56; 2 studies, N=98], 4g sulphasalazine may be more clinically effective at increasing clinical remission rates at >8 weeks compared to 2g olsalazine [very low quality, 1 study, N=56].

**Clinical improvement**

2g olsalazine may be more clinically effective at increasing clinical improvement rates compared to 4g sulphasalazine at 8 weeks, [very low quality evidence, 1 study, N=31; 1 study, N=42].

**Important outcomes**

Very low quality evidence showed there may be no clinical difference between 2g olsalazine and 4g sulphasalazine at 8 weeks in increasing endoscopic remission rates although 2g olsalazine may be more clinically effective at increasing clinical and endoscopic remission rates at 8 weeks. In contrast, 6g sulphasalazine may be more clinically effective at increasing clinical and endoscopic remission rates at 6 weeks compared to 3g olsalazine this effect was reversed at 12 weeks [very low quality evidence, 2 studies, N=83; 2 studies, N=83; 1 study, N=43; 1 study, N=53]. There may be no clinical difference between 2g olsalazine and 4g sulphasalazine in adverse event rates [very low quality, 1 study, N=37].

**5.18.1.12 Interclass comparison - Balsalazide versus mesalazine (all types)**

**Clinical remission and clinical improvement**

6.75g balsalazide may be more clinically effective in increasing clinical remission rates compared to 2.4g mesalazine at 2, 4, 8, 12 weeks and may be more clinically effective at increasing clinical improvement at 8 weeks. [very low quality evidence, 1 study, N=99; 2 studies, N=249; 1 study, N=99; 1 study, N=72].

### **Important outcomes**

6.75g balsalazide is more clinically effective at increasing clinical and endoscopic remission compared to 2.4g mesalamine at 4 weeks and may be more clinically effective at 8 and 12 weeks [very low quality evidence, 1=99; 3 studies, N=343; 1=99]. 6.75g balsalazide has fewer adverse events than 2.4g mesalamine, the entire range of the confidence interval did not show a clinically important difference between the two interventions [very low quality evidence, 3 studies, N=376]. There may be no clinical difference between 6.75g balsalazide and 2.4g mesalamine in serious adverse event rates [3 studies, N=376].

#### **5.18.1.13 Regimen comparison**

##### **Clinical remission**

High quality evidence showed there is no difference in clinical remission rates between once and three times daily ASAs and may not be between twice and four times daily ASAs. There is no difference in clinical improvement rates between two and four times daily ASAs [High quality to very low quality evidence, 1 study, N=360; 1 study, N=150; 1 study, N=150].

##### **Important outcomes**

There is no difference in endoscopic remission rates between once and three times daily ASAs [high quality evidence, 1 study, N=360]. There may be no difference in adverse or serious adverse events rates between one and three times daily ASAs [moderate to low quality evidence, 1 study, N=360, 1 study, N=360].

#### **5.18.1.14 Preparation comparison**

##### **Clinical remission**

There may be no difference in clinical remission rates at 3 weeks or in clinical improvement rates between mesalazine granules and tablet. There is no difference at 8 weeks in clinical remission rates [very low to low quality evidence, 1 study, N=229; 2 study, N=594; 3 studies, N=438].

##### **Important outcomes**

There may be no difference in endoscopic or clinical and endoscopic remission rates between mesalazine granules and tablets at 8 weeks [very low quality evidence, 1 study, N=357; 1 study, N=357]. Very low quality evidence showed there may be no difference in adverse or serious adverse event rates between mesalazine granules and tablets at 8 weeks [very low quality evidence, 1 study, N=153; 2 studies, N=594].

#### **5.18.2 Economic evidence statements**

One directly applicable economic study with potentially serious limitations found that in comparison to 2.4g/day of mesalazine, treatment with 2.4g/day of Mezavant XL mesalazine costs more but has yields outcomes, with the ICER being £749/QALY.

One directly applicable economic study with minor limitations found that in comparison to standard dose of mesalazine (2.4g/day), treatment with a high dose of mesalazine (4.8g/day) costs less and yields better outcomes.

One partially applicable economic study with potentially serious limitations found that in comparison to 2.4g-4.8g/day of mesalazine, treatment with 6.75g/day of balsalazide costs less and yields better outcomes.

## 5.19 Clinical evidence: Oral corticosteroids

A literature search identified 5 studies which looked at the use of oral corticosteroids compared to themselves and placebo<sup>13,122,167,180,207</sup> Evidence from the studies are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

The reviews in the following section are oral corticosteroids versus placebo (section 5.20.1) and oral corticosteroids versus oral corticosteroids comparisons (dose, regimen and preparation).

“Oral budesonide for induction of remission in ulcerative colitis” was published by the Cochrane collaboration in 2010<sup>199</sup>. The review included 3 studies which compared budesonide to prednisolone, mesalamine and placebo. The Cochrane review concluded that there was no evidence to recommend the clinical use of oral budesonide for the induction of remission in active colitis. The Cochrane review was excluded as it included drugs that are not currently available in the UK; budesonide MMX and did not specify the severity of disease. The following studies included in the Cochrane review were excluded from the Ulcerative Colitis review for the following reason:

- LOFTBERG1996; DHAENS2010: budesonide preparation is not available in the UK.

5.20 Evidence profile

5.20.1 Oral corticosteroids versus placebo

Table 53: Oral corticosteroids versus placebo

Quality assessment							No of patients		Effect		Qualit y	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecisio n	Other considerations	Oral corticosteroids	Placebo	Relative (95% CI)	Absolute		
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical and endoscopic remission up to 4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	9/19 (47.4%)	3/18 (16.7% )	RR 2.84 (0.91 to 8.86)	307 more per 1000 (from 15 fewer to 1000 more)	⊕⊕○○ LOW	IMPORTAN T

<sup>1</sup> Limitations comprised of unclear randomisation and allocation concealment.

<sup>2</sup> Crosses the 1.25 relative risk (RR) MID.

Table 54: Oral corticosteroids: dose comparison

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher dose	Lower dose	Relative (95% CI)	Absolute		
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement 0≤2 weeks - 40mg vs 20mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	18/20 (90%)	9/20 (45%)	RR 2 (1.21 to 3.32)	450 more per 1000 (from 95 more to 1000 more)	⊕⊕○○ LOW	CRITICAL
Clinical improvement 0≤2 weeks - 60mg vs 20mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	18/20 (90%)	9/20 (45%)	RR 2 (1.21 to 3.32)	450 more per 1000 (from 95 more to 1000 more)	⊕⊕○○ LOW	CRITICAL
Clinical improvement 0≤2 weeks - 60mg vs 40mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/20 (90%)	18/20 (90%)	RR 1 (0.81 to 1.23)	0 fewer per 1000 (from 171 fewer to 207 more)	⊕⊕⊕○ MODERATE	CRITICAL
clinical and endoscopic remission 0≤2 weeks - 40mg vs 20mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	10/20 (50%)	4/20 (20%)	RR 2.5 (0.94 to 6.66)	300 more per 1000 (from 12 fewer to 1000 more)	⊕⊕○○ LOW	IMPORTANT
clinical and endoscopic remission 0≤2 weeks - 60mg vs 20mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	10/20 (50%)	4/20 (20%)	RR 2.5 (0.94 to 6.66)	300 more per 1000 (from 12 fewer to 1000 more)	⊕⊕○○ LOW	IMPORTANT
clinical and endoscopic remission 0≤2 weeks - 60mg vs 40mg												

1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	10/20 (50%)	10/20 (50%)	RR 1 (0.54 to 1.86)	0 fewer per 1000 (from 230 fewer to 430 more)	⊕○○○ VERY LOW	IMPORTANT
<b>clinical and endoscopic remission end of treatment - 40mg vs 20mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	13/20 (65%)	6/20 (30%)	RR 2.17 (1.03 to 4.55)	351 more per 1000 (from 9 more to 1000 more)	⊕⊕○○ LOW	IMPORTANT
<b>clinical and endoscopic remission end of treatment - 60mg vs 20mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	13/20 (65%)	6/20 (30%)	RR 2.17 (1.03 to 4.55)	351 more per 1000 (from 9 more to 1000 more)	⊕⊕○○ LOW	IMPORTANT
<b>clinical and endoscopic remission end of treatment - 60mg vs 40mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	13/20 (65%)	13/20 (65%)	RR 1 (0.63 to 1.58)	0 fewer per 1000 (from 240 fewer to 377 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Hospitalisations: &gt;4≤6 weeks - 40mg vs 20mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	2/20 (10%)	0/20 0%	OR 7.79 (0.47 to 372.38) <sup>4</sup>	100 more per 1000 (from 50 fewer to 250 more) <sup>5</sup>	⊕○○○ VERY LOW	IMPORTANT
<b>Hospitalisations: &gt;4≤6 weeks - 60mg vs 20mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	1/20 (5%)	0/20 (0%)	OR 7.39 (0.15 to 372.38) <sup>4</sup>	50 more per 1000 (from 80 fewer to 180 more) <sup>5</sup>	⊕○○○ VERY LOW	IMPORTANT
<b>Hospitalisations: &gt;4≤6 weeks - 60mg vs 40mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	1/20 (5%)	2/20 (10%)	OR 0.50 (0.05 to 5.06) <sup>4</sup>	50 fewer per 1000 (from 210 fewer to 110 more) <sup>5</sup>	⊕○○○ VERY LOW	IMPORTANT
<b>adverse events - 40mg vs 20mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	4/20 (20%)	4/20 (20%)	RR 1 (0.29 to 3.45)	0 fewer per 1000 (from 142 fewer to 490 more)	⊕○○○ VERY LOW	IMPORTANT
<b>adverse events - 60mg vs 20mg</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	6/20 (30%)	4/20 (20%)	RR 1.5 (0.5 to 4.52)	100 more per 1000 (from 100 fewer to 704 more)	⊕○○○ VERY LOW	IMPORTANT

adverse events - 60mg vs 40mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	6/20 (30%)	4/20 (20%)	RR 1.5 (0.5 to 4.52)	100 more per 1000 (from 100 fewer to 704 more)	⊕○○○ VERY LOW	IMPORTANT
clinical improvement_ Beclometasone 10mgs vs 5mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	9/19 (47.4%)	9/19(47.4%)	RR 1.00 (0.51 to 1.95)	0 more per 1000 (from 232 fewer to 450 more)	⊕○○○ VERY LOW	IMPORTANT
adverse events_ Beclometasone 10mgs vs 5mg												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	2/19 (10.5%)	0/19 (0.5%)	OR 7.81 (0.47 to 129.75) <sup>4</sup>	22 more per 1000 (from 4 fewer to 379 more) <sup>5</sup>	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Limitations comprised of unclear randomisation and allocation concealment.

<sup>2</sup> Crosses the 1.25 relative risk (RR) MID.

<sup>3</sup> Crosses the 0.75 and 1.25 relative risk (RR) MIDs .

<sup>4</sup> Peto odds ratio

<sup>5</sup> Risk difference

**Table 55: Oral corticosteroids: regimen comparison**

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Once a day	Four times a day	Relative (95% CI)	Absolute	Quality	Importance
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
clinical remission 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/23 (13%)	5/22 (22.7%)	RR 0.57 (0.16 to 2.12)	98 fewer per 1000 (from 191 fewer to 255 more)	⊕○○○ VERY LOW	CRITICAL
clinical improvement 0≤2 weeks												

1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	14/23 (60.9%)	12/22 (54.5%)	RR 1.12 (0.67 to 1.85)	65 more per 1000 (from 180 fewer to 464 more)	⊕○○○ VERY LOW	CRITICAL
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<sup>1</sup> Limitations comprised of unclear randomisation, allocation concealment, single blinding.

<sup>2</sup> Crosses 0.75 and 1.25 relative risk (RR) MIDs.

**Table 56: Oral corticosteroids: preparation comparison**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral	IM	Relative (95% CI)	Absolute		
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
clinical remission – 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	18/19 (94.7%)	18/21 (85.7%)	RR 1.11 (0.90 to 1.36)	94 more per 1000 (from 86 fewer to 309more)	⊕⊕○○ LOW	CRITICAL
clinical remission - >6≤8 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	18/91 (94.7%)	18/21 (85.7%)	RR 1.11 (0.90 to 1.36)	94 more per 1000 (from 86 fewer to 309 more)	⊕⊕○○ LOW	CRITICAL
adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	5/19 (26.3%)	1/21 (4.8%)	RR 5.53 (0.71 to 43.16)	216 more per 1000 (from 14 fewer to 1000 more)	⊕⊕○○ LOW	IMPORTANT

<sup>1</sup> Limitations comprised of unclear allocation concealment.  
<sup>2</sup> Crosses 1.25 relative risk (RR) MID.

## 5.21 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 5.22 Evidence statements

### 5.22.1 Clinical evidence statements

#### 5.22.1.1 Oral corticosteroids versus placebo

No evidence was identified on clinical remission, clinical improvement or quality of life.

##### Important outcomes

Oral corticosteroids (prednisone) may be more clinically effective in increasing clinical and endoscopic remission rates at up to 4 weeks than placebo [low quality evidence, 1 study, N=37].

#### 5.22.1.2 Dose comparison

##### Clinical improvement

60mg and 40mg prednisolone are both more clinically effective at increasing clinical improvement rates at 4 weeks compared to 20mg, there is no difference between 60mg and 40mg (low quality evidence, 1 study, n=40)

##### Important outcomes

60mg and 40mg prednisolone may be more clinically effective at increasing clinical and endoscopic remission rates at 2 weeks and at the end of trial compared to 20mg prednisolone, there is no difference between 60mg and 40mg. There is no difference in hospitalisations or in adverse events between any of the doses [very low and low quality evidence, 1 study, N=40].

#### 5.22.1.3 Beclometasone

No evidence was identified on clinical remission or quality of life.

##### Clinical improvement

There may be no clinically important difference in clinical improvement rates between 5mg and 10mg of beclometasone (very low quality evidence, N=38).

##### Important outcomes

There may be no clinically important difference in adverse event rates between 5mg and 10mg beclometasone (very low quality evidence, N=38).

#### **5.22.1.4 Regimen comparison**

##### **Clinical remission**

There may be no clinically important difference in clinical remission or clinical improvement rates between once and four times daily prednisolone [very low quality evidence, 1 study, N=45].

#### **5.22.1.5 Route comparison**

##### **Clinical remission**

There may be no clinical difference in clinical remission rates between oral and IM corticosteroids [low quality evidence, 1 study, N=40].

##### **Important outcomes**

Oral corticosteroids may have higher clinically important adverse event rates compared to IM corticosteroids [very low quality evidence, 1 study, N=40].

#### **5.22.2 Economic evidence statements**

No relevant economic evaluations were identified.

### **5.23 Clinical evidence: Oral aminosalicylates versus oral corticosteroids**

A literature search identified 7 studies<sup>28,79,80,122,179,180,183</sup> which looked at the use of oral aminosalicylates compared to steroids and a combination of oral aminosalicylates and steroids. Two papers reported the same study data<sup>79,80</sup>.

## 5.24 Evidence profile

### 5.24.1 Oral aminosalicylates versus oral corticosteroids

Table 57: Oral aminosalicylates versus oral corticosteroids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA	Oral Steroid	Relative (95% CI)	Absolute		
Clinical remission ->2≤4 weeks												
2	randomised trials	very serious <sup>1</sup>	very serious <sup>2</sup>	no serious indirectness	serious <sup>3</sup>	none	55/95 (57.9%)	58/88 (65.9%)	RR 0.88 (0.69 to 1.11)	79 fewer per 1000 (from 204 fewer to 73 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >6≤8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	91/166 (54.8%)	70/177 (39.5%)	RR 1.39 (1.1 to 1.74)	154 more per 1000 (from 40 more to 293 more)	⊕⊕⊕○ MODERATE	CRITICAL
Clinical improvement -> 2≤4 weeks												
1	randomised trials	very serious <sup>1,5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/80 (73.8%)	57/73 (78.1%)	RR 0.94 (0.79 to 1.13)	47 fewer per 1000 (from 164 fewer to 102 more)	⊕⊕○○ LOW	CRITICAL
Clinical improvement - >6≤8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/166 (85.5%)	136/177 (76.8%)	RR 1.11 (1.01 to 1.23)	85 more per 1000 (from 8 more to 177 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - >6≤8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	105/166 (63.3%)	88/177 (49.7%)	RR 1.27 (1.05 to 1.54)	134 more per 1000 (from 25 more to 268 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Endoscopic remission - >8 weeks												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	4/15 (26.7%)	11/15 (73.3%)	RR 0.36 (0.15 to 0.89)	469 fewer per 1000 (from 81 fewer to 623 fewer)	⊕⊕○○ LOW	IMPORTANT
Clinical and endoscopic remission ->2≤4 weeks												
1	randomised	very serious <sup>7</sup>	no serious	no serious	serious <sup>3</sup>	none	2/20	9/20	RR 0.22	351 fewer per 1000	⊕○○○	IMPORTANT



	trials		inconsistency	indirectness			(10%)	(45%)	(0.05 to 0.9)	(from 45 fewer to 427 fewer)	VERY LOW	
<b>Adverse events</b>												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3,4</sup>	none	41/253 (16.2%)	45/267 (16.9%)	RR 0.97 (0.67 to 1.4)	5 fewer per 1000 (from 56 fewer to 67 more)	⊕⊕○○ LOW	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3,4</sup>	none	2/166 (1.2%)	3/177 (1.7%)	RR 0.71 (0.12 to 4.2)	5 fewer per 1000 (from 15 fewer to 54 more)	⊕⊕○○ LOW	IMPORTANT

<sup>1</sup> Single blind or open. Overall unclear method of randomisation and allocation concealment. Limited or unbalanced baseline characteristics.

<sup>2</sup>  $I^2 > 75\%$ .

<sup>3</sup> Crosses the lower 0.75 relative risk (RR) MID.

<sup>4</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>5</sup> Single blind, uneven baseline characteristics and >10% difference in missing data between the treatment arms.

<sup>6</sup> Open study. Overall unclear method of randomisation and allocation concealment. Limited baseline characteristics.

<sup>7</sup> Unclear allocation concealment. Open study. Very basic assessment of symptoms. No index used.

#### Additional narrative information which could not be meta-analysed:

In the LENNARDJONES1960<sup>122</sup> study the adverse events were given at the end of one year and so it did not meet the inclusion criteria. There were 17/51 in the prednisolone arm (from both stages of the trial) and 12/20 in the SASP arm who suffered from adverse events over this time period (see the evidence table for further details on the adverse events experienced).

#### Subgroup analysis

Heterogeneity (79%) was present for the clinical remission outcome between two studies, CAMPIERI2003<sup>28</sup> and ROMANO2010<sup>183</sup>. The main difference was the age of the populations. The ROMANO2010<sup>183</sup> paper was a paediatric study which found the oral steroids to have a greater clinical remission rate, whereas the adult study CAMPIERI2003<sup>28</sup> found no difference between oral ASAs and oral steroids. See Table 58 for the differences between the studies.

**Table 58: Oral ASAs versus oral Steroids: Clinical remission at >2≤4 weeks**

Study	Severity of disease	Extent of disease	Drug (mechanism of release) & dose	Age
CAMPIERI2003	Mild to moderate	Extensive or left-sided	2.4g 5-ASA (Asacol) and 5mg beclometasone	18-70 years
ROMANO2010	Mild to moderate	Left sided or pancolitis	80mg/kg/day 5-ASA (Asacol) and 5mg/day beclometasone	<18 years

Table 59: Oral aminosalicylates and oral steroid combination versus oral aminosalicylates

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA & steroid	Oral ASA & placebo	Relative (95% CI)	Absolute		
Clinical remission - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	34/58 (58.6%)	21/61 (34.4%)	RR 1.7 (1.13 to 2.56)	241 more per 1000 (from 45 more to 537 more)	⊕⊕⊕⊕ LOW	CRITICAL
Clinical improvement - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	44/58 (75.9%)	31/61 (50.8%)	RR 1.49 (1.12 to 1.99)	249 more per 1000 (from 61 more to 503 more)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life-> 2≤4 weeks												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	18/58 (31%)	10/61 (16.4%)	RR 1.89 (0.95 to 3.75)	146 more per 1000 (from 8 fewer to 451 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	1/58 (1.7%)	3/61 (4.9%)	RR 0.35 (0.04 to 3.27)	32 fewer per 1000 (from 47 fewer to 112 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

1 The difference in the proportion of missing data is >10% between the treatment arms.

2 Crosses the upper 1.25 relative risk (RR) MID.

3 Crosses the lower 0.75 relative risk (RR) MID.

## 5.25 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 5.26 Evidence statements

### 5.26.1 Clinical evidence statements

#### 5.26.1.1 Oral aminosalicylates versus oral corticosteroids

##### Clinical remission

There may be no clinical difference between oral ASAs and oral steroids (beclometasone) at increasing clinical remission rates at  $>2\leq 4$  weeks [very low quality evidence, 2 studies, N=183]. Oral ASAs may be more clinically effective at increasing clinical remission rates compared to oral steroids at  $>6\leq 8$  weeks [moderate quality evidence, 1 study, N= 343].

##### Clinical improvement

There may be no clinical difference in clinical improvement rates between oral ASAs and oral steroids (beclometasone) at  $>2\leq 4$  weeks or  $>6\leq 8$  weeks [very low to high quality evidence 2 studies, N=200; 1=343].

##### Important outcomes

Oral ASAs may be more clinically effective at increasing endoscopic remission compared to oral steroids (Budesonide) at  $>6\leq 8$  weeks [moderate quality evidence, 1 study, N=343] conversely oral ASAs may be more clinically effective at increasing endoscopic remission compared to oral steroids (Beclometasone) at  $>8$  weeks [low quality evidence, 1 study, N=30]. Oral steroids (prednisolone) may be more clinically effective at increasing clinical and endoscopic remission rates at 3-4 weeks compared to oral ASAs [ very low quality evidence, 1 study, N=40].

##### Adverse events

There may be no clinical difference in adverse event rates between oral ASAs and oral steroids (beclometasone and Budesonide) or in serious adverse events (Budesonide) [very low to low quality evidence, 3 studies, N=577; 1 study, N=343]

#### 5.26.1.2 Oral aminosalicylates plus corticosteroids versus oral aminosalicylates plus placebo

##### Clinical remission

Oral ASA plus steroids (mesalazine (Asacol) and beclometasone) may be more clinically effective at increasing clinical remission and clinical improvement rates compared to oral ASAs plus placebo at 4 weeks [low quality evidence, 1 study, N=119].

##### Important outcomes

Oral ASA plus steroids (mesalazine (Asacol) and beclometasone) maybe more clinically effective at increasing endoscopic remission rates compared to oral ASAs plus placebo [low quality evidence, 1 study, N=119]. There may be no clinical difference in adverse event rates between oral ASAs and oral steroids (mesalazine (Asacol) and beclometasone) compared to oral ASAs (mesalazine (Asacol)) and placebo [very low quality evidence, 1=119].

#### **5.26.2 Economic evidence statements**

No relevant economic evaluations were identified.

### **5.27 Clinical evidence: Topical aminosalicylates versus oral aminosalicylates**

Six studies were included in the review.<sup>41,72,139,170,224,225</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

## 5.28 Evidence profile

### 5.28.1 Topical aminosalicylates versus oral aminosalicylates

**Table 60: Topical aminosalicylates versus oral aminosalicylates**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA	Topical ASA	Relative (95% CI)	Absolute		
Clinical remission - 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	6/29 (20.7%)	18/29 (62.1%)	RR 0.33 (0.15 to 0.72)	416 fewer per 1000 (from 174 fewer to 528 fewer)	⊕⊕OO LOW	CRITICAL
Clinical remission - >2≤4 weeks												
2	randomised trials	serious <sup>1,3</sup>	very serious <sup>4</sup>	serious <sup>2</sup>	serious <sup>5</sup>	none	35/69 (50.7%)	52/67 (77.6%)	RR 0.65 (0.5 to 0.86)	272 fewer per 1000 (from 109 fewer to 388 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical remission - >6≤8 weeks												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>6</sup>	none	24/40 (60%)	19/38 (50%)	RR 1.2 (0.8 to 1.8)	100 more per 1000 (from 100 fewer to 400 more)	⊕OOO VERY LOW	CRITICAL
Clinical improvement - 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	5/29 (17.2%)	19/29 (65.5%)	RR 0.26 (0.11 to 0.61)	485 fewer per 1000 (from 256 fewer to 583 fewer)	⊕⊕OO LOW	CRITICAL
Clinical improvement - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	10/29 (34.5%)	24/29 (82.8%)	RR 0.42 (0.25 to 0.71)	480 fewer per 1000 (from 240 fewer to 621 fewer)	⊕⊕OO LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission - 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	4/29 (13.8%)	15/29 (51.7%)	RR 0.27 (0.1 to 0.71)	378 fewer per 1000 (from 150 fewer to 466 fewer)	⊕⊕OO LOW	IMPORTANT
Endoscopic remission - >2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>5</sup>	none	10/29 (34.5%)	21/29 (72.4%)	RR 0.48 (0.27 to 0.83)	377 fewer per 1000 (from 123 fewer to 529 fewer)	⊕OOO VERY LOW	IMPORTANT
Endoscopic remission - >6≤8 weeks												

1	randomised trials	serious <sup>3</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>5,6</sup>	none	18/40 (45%)	14/38 (36.8%)	RR 1.22 (0.71 to 2.09)	81 more per 1000 (from 107 fewer to 402 more)	⊕○○○ VERY LOW	IMPORTANT
<b>Adverse events</b>												
2	randomised trials	serious <sup>1,3</sup>	very serious <sup>4</sup>	serious <sup>2</sup>	very serious <sup>5,6</sup>	none	12/69 (17.4%)	11/68 (16.2%)	RR 1.07 (0.51 to 2.23)	11 more per 1000 (from 79 fewer to 199 more)	⊕○○○ VERY LOW	IMPORTANT

1 Single investigator blind. Unclear method of randomisation.

2 Risk of an indirect population as it may include patient with severe disease.

3 >10% difference in missing data between the treatment arms.

4  $I^2 > 75\%$ .

5 95% CI Crosses the lower 0.75 relative risk (RR) MID.

6 95% CI Crosses the upper 1.25 relative risk (RR) MID.

### Subgroup analysis

For both clinical remission at >2≤4weeks and adverse events, heterogeneity (77% & 81% respectively) was present between the same two studies, GIONCHETTI1998<sup>72</sup> and PRANTERA2005<sup>170</sup>. See Table 61 for differences between the studies.

**Table 61: Topical aminosalicylates versus oral aminosalicylates clinical remission**

Study	Dose (per day) and preparation	Severity	Extent	Age
GIONCHETTI1998	2.4g oral mesalazine (Asacol) versus 1.2g rectal mesalazine suppositories	DAI >3, not upper limit	Active ulcerative proctitis not extending beyond 15cm from anus	>18 years
PRANTERA2005	3.6g oral mesalazine (Mezavant XL) versus 4g rectal mesalazine liquid enema (Asacol)	CAI≥6	Left sided UC (≥15cm but no further than the splenic flexure)	>18 years

There are a couple of reasons that may explain the heterogeneity; GIONCHETTI1998<sup>72</sup> favours the use of topical ASAs for both outcomes and has a population with only proctitis and uses suppositories for the rectal mesalazine preparation. The PRANTERA2005<sup>170</sup> study uses a higher dose of oral mesalazine and has more extensive disease favouring the use of an oral ASA over a liquid ASA enema.

**Table 62: Oral aminosalicylates versus oral and topical aminosalicylates**

Quality assessment	No of patients	Effect	Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA	Oral ASA & topical ASA	Relative (95% CI)	Absolute		
<b>Clinical remission - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,4</sup>	none	16/47 (34%)	25/57 (43.9%)	RR 0.78 (0.47 to 1.27)	96 fewer per 1000 (from 232 fewer to 118 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical remission - &gt;4≤6 weeks</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/67 (82.1%)	55/63 (87.3%)	RR 0.94 (0.81 to 1.09)	52 fewer per 1000 (from 166 fewer to 79 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Clinical remission at 8 weeks (4 weeks of combination treatment, 4 weeks of oral treatment)</b>												
1	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	20/47 (42.6%)	37/58 (63.8%)	RR 0.67 (0.45 to 0.98)	211 fewer per 1000 (from 13 fewer to 351 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical improvement - &gt;2≤4 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	29/47 (61.7%)	51/57 (89.5%)	RR 0.69 (0.54 to 0.88)	277 fewer per 1000 (from 107 fewer to 412 fewer)	⊕⊕○○ LOW	CRITICAL
<b>Clinical improvement - &gt;4≤6 weeks</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/67 (85.1%)	57/63 (90.5%)	RR 0.94 (0.83 to 1.07)	54 fewer per 1000 (from 154 fewer to 63 more)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Clinical improvement &gt;6≤8 weeks (4 weeks of combination treatment, 4 weeks of oral treatment)</b>												
1	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	32/47 (68.1%)	50/58 (86.2%)	RR 0.79 (0.63 to 0.99)	181 fewer per 1000 (from 9 fewer to 319 fewer)	⊕○○○ VERY LOW	CRITICAL
<b>Quality of life_EQ5D - 0≤2 weeks (oral &amp; rectal) (Better indicated by lower values)</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	71	-	MD 0.02 lower (0.08 lower to 0.05 higher)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Quality of life_EQ5D - &gt;2≤4 weeks (oral &amp; rectal) (Better indicated by lower values)</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	71	-	MD 0.07 lower (0.13 lower to 0 higher)	⊕⊕⊕○ MODERATE	CRITICAL
<b>Quality of life_EQ5D - &gt;6≤8 weeks (4 weeks of combination treatment, 4 weeks of oral treatment) (Better indicated by lower values)</b>												
1	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	71	-	MD 0.05 lower (0.11 lower to 0.01 higher)	⊕⊕○○ LOW	CRITICAL
<b>Endoscopic remission - &gt;4≤6 weeks</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	36/62 (58.1%)	41/58 (70.7%)	RR 0.82 (0.63 to 1.07)	127 fewer per 1000 (from 262 fewer to 49 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Adverse events (6 weeks combination treatment)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>2,4</sup>	none	5/67 (7.5%)	4/63 (6.3%)	RR 1.18 (0.33 to 4.18)	11 more per 1000 (from 43 fewer to 202 more)	⊕⊕OO LOW	IMPORTANT
Adverse events (4 weeks of combination treatment, 4 weeks of oral treatment)												
1	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	28/56 (50%)	24/71 (33.8%)	RR 1.48 (0.97 to 2.25)	162 more per 1000 (from 10 fewer to 423 more)	⊕OOO VERY LOW	IMPORTANT
Serious adverse events (4 weeks of combination treatment, 4 weeks of oral treatment)												
1	randomised trials	very serious <sup>1,3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,4</sup>	none	1/56 (1.8%)	3/71 (4.2%)	RR 0.42 (0.05 to 3.95)	25 fewer per 1000 (from 40 fewer to 125 more)	⊕OOO VERY LOW	IMPORTANT

1 Unclear method randomisation and allocation concealment.

2 95% CI Crosses the lower 0.75 relative risk (RR) MID.

3 >10% difference in missing data between the two treatment arms at 8 weeks.

4 95% CI Crosses the upper 1.25 relative risk (RR) MID.

**Table 63: Oral aminosalicylates & topical aminosalicylates versus oral aminosalicylates & topical aminosalicylates**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASA & lower dose topical ASA	Oral ASA & higher dose topical ASA	Relative (95% CI)	Absolute		
Clinical remission												
0	no evidence available					none	-	-	-	-		CRITICAL
Clinical improvement												
0	no evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Colectomy - 1g versus 2g>8 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/9 (0%)	1/10 (10%)	OR <sup>3</sup> 0.15 (0 to 7.58)	84 fewer per 1000 (from 100 fewer to 357 more) <sup>4</sup>	⊕○○○ VERY LOW	IMPORTANT
Colectomy - 1g versus 4g>8 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	0/9 (0%)	2/12 (16.7%)	OR <sup>3</sup> 0.16 (0.01 to 2.8)	136 fewer per 1000 (from 165 fewer to 192 more) <sup>4</sup>	⊕○○○ VERY LOW	IMPORTANT
Colectomy - 2g versus 4g>8 weeks												



1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/10 (10%)	2/12 (16.7%)	OR <sup>3</sup> 0.58 (0.05 to 6.35)	63 fewer per 1000 (from 157 fewer to 393 more) <sup>4</sup>	⊕○○○ VERY LOW	IMPORTANT
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<sup>1</sup> Single blind. Overall unclear method of randomisation and allocation concealment. Limited baseline characteristics.

<sup>2</sup> 95% CI crosses both the lower 0.75 and upper 1.25 MIDs.

<sup>3</sup> Peto odds ratio.

<sup>4</sup> Risk difference.

## 5.29 Economic evidence

### Published literature

One study<sup>39</sup> was included that addressed oral ASAs versus oral ASA plus rectal ASAs. This is summarised in the economic evidence profile below. See also the study selection flow chart in Appendix E and study evidence tables in Appendix G.

No studies that met the inclusion criteria were selectively excluded.

**Table 64: Economic evidence profile: oral ASA versus oral and topical ASA**

Study	Limitations	Applicability	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Connolly <sup>39</sup>	Minor limitations	Directly applicable	Relative treatment effect was obtained from one study.	-£578	0.01 QALYs	Combination therapy dominates (less costly and more effective)	Combination therapy showed a higher probability of being cost-effective over a threshold range of £0 - £20,000.

### **New cost-effectiveness analysis**

Note that this area was prioritised for new cost-effectiveness analysis. This will look at the most cost-effective treatment sequence for induction of remission.

## **5.30 Evidence statements**

### **5.30.1 Clinical evidence statements**

#### **5.30.1.1 Oral versus topical aminosalicylates**

##### **Clinical remission**

Topical ASAs are more clinically effective at increasing clinical remission rates than oral ASAs at 0≤2 weeks and >2≤4 weeks and >6≤8 weeks, they may be more effective at >8 weeks [Low and very low quality evidence, 1 study, N=58, 2 studies N=136].

##### **Clinical improvement**

Topical ASAs are more clinically effective at increasing clinical improvement rates than oral ASAs at 0≤2 and 2≤4 weeks [low quality evidence, 2 studies, N=95; 1 study, N=37].

##### **Important outcomes**

Topical ASAs are more clinically effective at increasing endoscopic remission rates than oral ASAs at 0≤2 weeks and >2≤4 weeks, though there may be no clinically difference at >6≤8 weeks [low and very low quality evidence, 1 study, N=58; 1 study, N=78]. There may be no clinical difference between oral and topical ASAs for adverse event rates [very low quality evidence, 2 studies, N=137].

#### **5.30.1.2 Oral aminosalicylates versus oral aminosalicylates plus topical aminosalicylates**

##### **Clinical remission**

Oral ASA and topical ASA may be more clinically effective at increasing clinical remission rates at >2≤4 weeks compared to oral ASA alone [very low quality, 1 study, N=104].

There is no clinically important difference in clinical remission rates at 4≤6 weeks between oral ASA versus oral ASA & topical ASA [high quality evidence, 1 study, N=110].

Oral ASA & topical ASA for 4 weeks followed by oral ASA alone may be more clinically effective at increasing clinical remission rates at 8 weeks than oral ASA alone [very low quality evidence, 1 study, N=105].

##### **Clinical improvement**

Oral ASA and topical ASA may be more clinically effective at increasing clinical improvement rates at 4 weeks compared to oral ASA alone [low quality evidence, 1 study, N=104].

There is no clinically important difference in clinical improvement rates at 4≤6 weeks between oral ASA versus oral ASA & topical ASA [high quality evidence, 1 study, N=130].

Oral ASA & topical ASA for 4 weeks followed by oral ASA alone may be more clinically effective at increasing clinical improvement rates at 8 weeks than oral ASA alone [very low quality evidence, 1 study, N=105].

##### **Quality of life**

There is no clinically important difference in quality of life scores at 2, 4 and 8 weeks between oral ASA versus oral ASA & topical ASA (rectal ASA only used for the first 4 weeks) [Moderate and low quality evidence, 1 study, N=127].

#### **Important outcomes**

Oral & topical ASA may be more clinically effective at increasing endoscopic remission rates compared to oral ASAs alone at >4≤6 weeks [moderate quality evidence, 1 study, N=120]. Oral ASAs may have higher clinically important adverse event rates compared to oral ASAs & topical ASA (rectal ASA only used for the first 4 weeks) [very low quality evidence, 1 study, N=127]. There is no clinically important difference in adverse event rates between oral ASAs and oral & topical ASAs [low quality evidence, 1 study, N=130; 1 study, N=127]. There may be no clinically important difference in serious adverse events rates between oral ASAs and oral ASA & topical ASAs [very low quality evidence, 1 study, N=127].

#### **5.30.1.3 Oral plus topical aminosalicylates: dose comparison**

No evidence was identified on clinical remission, clinical improvement or quality of life.

#### **Important outcome**

There may be no clinically important difference in colectomy rates in oral ASA and 1g versus 2g or 4g of topical ASAs, [very low quality evidence, 1 study, N=19]. Oral ASA and 2g of topical ASA may have a clinically lower rate of colectomies compared to oral ASA & 4g of topical ASA, the direction of the estimate of effect, the direction of the estimate of effect does not favour either dose [very low quality evidence, 1 study, N=19].

#### **5.30.2 Economic evidence statements**

One directly applicable economic study with minor limitations found that in comparison to oral mesalazine (4g/day), treatment with oral mesalazine (4g/day) and topical mesalazine (1g/100ml) costs less and yields better outcomes.

### **5.31 Clinical evidence: Topical corticosteroids versus oral corticosteroids**

No relevant clinical studies comparing oral steroids with topical steroids or any other combination of oral/topical steroids and oral aminosalicylates were identified.

### **5.32 Economic evidence**

#### **Published literature**

No relevant economic evaluations were identified.

#### **New cost-effectiveness analysis**

New analysis was not prioritised for this area.

### **5.33 Evidence statements**

#### **5.33.1 Clinical evidence statements**

No relevant clinical studies were identified.

### 5.33.2 Economic evidence statements

No relevant economic evaluations were identified.

## 5.34 Network meta-analysis

Two network meta-analyses (NMAs) were performed; a baseline NMA which compared all treatments and a combined NMA which addressed the relationship between low and high doses of aminosalicylates. The combined NMA informed the inputs in the original health economic models which are described in Appendix L. For detailed explanation on methodology and results of the NMAs refer to Appendix I.

### 5.34.1 Comparison of the induction of remission treatments (baseline NMA)

A network meta-analysis (NMA) was performed to compare the treatments for the induction of remission in people with mild to moderate left-sided/extensive ulcerative colitis. The analyses were based on a total of 28 studies. These studies formed three networks of evidence for the outcomes: clinical remission, clinical improvement and withdrawals due to adverse events. These outcomes were considered by the GDG as the most important clinical outcomes. Withdrawals due to adverse events rather than drug related adverse events were chosen due to unclear reporting in the trials. Although this was not an outcome in the clinical review, it was chosen because it is thought to be a good approximate measure for this outcome. The interventions included in each network are shown in Table 65. For more details on the network please see appendix I.

**Table 65: Induction of remission treatments included in the network meta-analyses of people with mild to moderate left sided and extensive ulcerative colitis**

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

### 5.34.2 Evidence summary

#### Clinical remission

A NMA of 20 studies comparing 10 treatments suggested that oral mesalazine and beclometasone has the highest probability of being the best treatment (67%), oral prednisolone the second (24%) and oral and topical mesalazine the third (7%). The other treatments (placebo, low dose mesalazine, high dose mesalazine, high dose olsalazine, balsalazide, beclometasone, low dose sulphasalazine) all had a less than 1% probability of being the best treatment.

### Clinical improvement

A NMA of 23 studies comparing 9 treatments suggested that oral mesalazine and beclometasone has the highest probability of being the best treatment (63%), oral and topical mesalazine the second (36%) and high dose olsalazine the third (1%). The other treatments (placebo, low dose mesalazine, high dose mesalazine, low dose sulphasalazine, balsalazide, and beclometasone) all had a less than 1% probability of being the best treatment.

### Withdrawal from adverse events

A NMA of 24 studies comparing 9 treatments suggested that oral mesalazine and beclometasone has the highest probability of being the best treatment (63%) for the fewest withdrawals due to adverse events, balsalazide the second (12%), oral beclometasone the third (6%), oral and topical mesalazine the fourth (5%), high dose mesalazine the fifth (2%), and low dose sulphasalazine the sixth (1%). The other treatments (placebo, low dose mesalazine, high dose olsalazine) all had a less than 1% probability of being the best treatment.

### 5.34.3 Comparison of the induction of remission treatments with the aminosalicylates combined into low and high doses (combined NMA)

A NMA combining the aminosalicylates was performed following the results of the baseline NMA. This was done to look at the relationship between low and high dose aminosalicylates, beclometasone dipropionate and the combination treatments (i.e. oral mesalazine and oral beclometasone dipropionate, oral mesalazine and topical mesalazine). The analysis informed the inputs into the original health economic model.

The analyses were based on a total of 17 studies. These studies formed two networks of evidence for the two outcomes: clinical remission and number of withdrawals. The outcomes used in the health economic model consisted of clinical remission and withdrawals due to adverse events, so for the combined NMA, clinical improvement was not analysed. Withdrawals due to adverse events rather than drug related adverse events were chosen due to unclear reporting in the trials. Although this was not an outcome in the clinical review, it was chosen because it is thought to be a good approximate measure for this outcome. The interventions included in each network are shown in Table 66. For more details on the network please see Appendix I.

**Table 66: Induction of remission treatments (combined aminosalicylates) included in the network meta-analyses of people with mild to moderate left sided and extensive ulcerative colitis**

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

#### **5.34.4 Evidence summary**

##### **Clinical remission**

A NMA of 17 studies comparing 7 treatments suggested that oral mesalazine and beclometasone has the highest probability of being the best treatment (64%), oral prednisolone the second (28%) and oral and topical mesalazine the third (7%). The other treatments (placebo, low dose mesalazine, high dose mesalazine, beclometasone, low dose sulphasalazine) all had a less than 1% probability of being the best treatment.

##### **Withdrawal from adverse events**

A NMA of 19 studies comparing 6 treatments suggested that oral mesalazine and beclometasone has the highest probability of being the best treatment (80%) for the fewest withdrawals due to adverse events, oral and topical mesalazine the second (7%), high dose ASA (6%) joint third with oral beclometasone (6%). Placebo had less than 1% probability of being the best treatment.

### **5.35 Health economic induction model summary**

#### **5.35.1 Original economic analysis**

The GDG considered studies<sup>25,26,132</sup> published on cost-effectiveness of aminosalicylates. They noted that these studies help to highlight the cost-effectiveness of specific aminosalicylates (ASAs) or ASA doses. However, other ASAs are available which have not been addressed. In addition, the studies modelled different treatment sequences after failure of first line treatment. The GDG considered that there are other clinically relevant sequences that were captured and hence this topic was considered to be a top priority for original economic analysis. The original economic model sought to address the various treatment options available for the induction of remission in people with mild to moderate left sided or extensive ulcerative colitis. A summary of the analysis is presented below and a full description can be found in Appendix L.

#### **5.35.2 Methods**

##### **5.35.2.1 Model overview**

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services (PSS) perspective. A decision tree was constructed in order to estimate the costs and QALYs associated with different treatment strategies for the induction of treatment. Uncertainty was explored through probabilistic and univariate sensitivity analyses. The time horizon considered in the base case model was 28 weeks. This was set to reflect the longest treatment sequence in the model which consists of five lines of treatment.

##### **5.35.2.2 Population**

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



### 5.35.2.3 Comparators

The comparators examined in the model are treatment sequences chosen by the GDG. The GDG considered the suitability of the drugs for use in patients with mild to moderate left sided or extensive ulcerative colitis and current clinical practice when compiling the treatment sequences. Based on the studies reviewed in the induction of remission chapter, two network meta-analyses (NMAs) were conducted addressing the treatments for the induction of remission (Appendix I). A baseline NMA was conducted which addressed three outcomes; clinical remission, clinical improvement and withdrawals due to adverse events. The NMA showed that there was no clinically significant difference between individual oral ASAs in terms of their effectiveness in inducing clinical remission. However, a dose effect observed. A second NMA was conducted (combined NMA) which pooled trials reporting low dose oral ASAs into one treatment group, and trials reporting high dose oral ASAs into another treatment group. The results of the combined NMA informed the clinical inputs in this economic analysis. In the analysis, ten treatment strategies were compared and are summarised in Table 67.

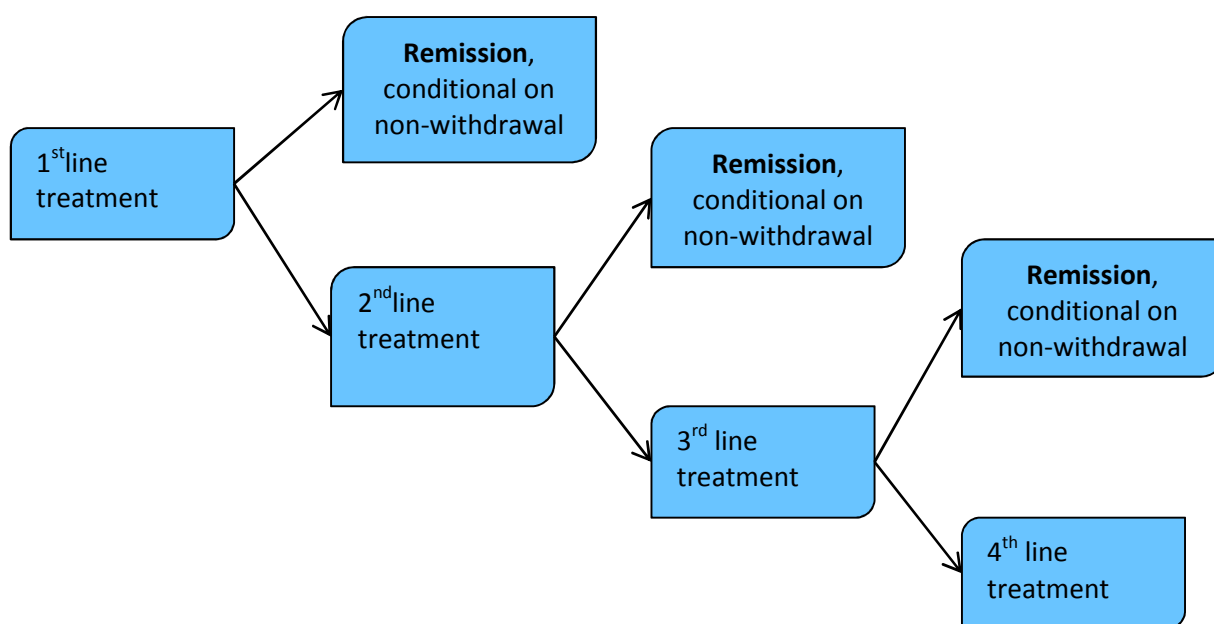
**Table 67: Treatment strategies in the model**

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

### 5.35.2.4 Model structure

A decision tree was constructed in which the QALY gain is driven by the proportion of people in whom remission is successfully induced. Author reported definitions of remission were used in line with the clinical review. Remission was conditional on not having withdrawn from therapy due to adverse events. People who withdrew or failed to respond to therapy at the end of a course of treatment moved on to the next treatment in the sequence. The GDG were aware that specific adverse events could be attributed to certain drugs included in the model. They however concluded that the reporting of adverse events in the RCTs was not sufficient to model specific treatment related adverse events. Withdrawal from treatment was therefore used as a proxy for adverse events. This implies that the costs and dis-utilities pertaining to adverse events for each treatment would be captured by the cost of treating withdrawals and the associated utility loss from remaining in active disease. To capture the benefits of inducing remission early, patients in whom remission is induced on the first line of treatment will gain more QALYs than those who respond on subsequent lines of treatment. The structure of the model is shown in Figure 3.

**Figure 3: Model structure**



#### 5.35.2.5 Model inputs

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs were validated by the GDG.

To parameterise treatment effects in the model, a network meta-analysis (NMA) based on a conditional logistic regression was carried out. The NMA provided treatment specific odds ratios for withdrawal and remission conditional on not withdrawing.

#### 5.35.2.6 Sensitivity analysis

In total, seven uni-variate sensitivity analyses were conducted, whereby, for each analysis one key model input was changed in order to explore the sensitivity of model results to changes in that parameter.

One multi-variate sensitivity analysis was conducted deterministically to address the effects of ASA costs on the model results.

A probabilistic analysis was carried out whereby distributions were assigned to treatment effects, utilities and, where possible, costs in order to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.

### 5.35.3 Results

#### 5.35.3.1 Base case

The results showed that the cost-effective option is strategy 10 as it yields the highest net monetary benefit (NMB). The strategy comprises of first line treatment with a high dose oral ASA with therapy

escalated in the following sequence in the event of treatment failure; high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery. Table 68 shows the breakdown of results. The probabilistic results allowed a ranking of the net monetary benefit to be developed and also showed the probability of an intervention being cost-effective out of 1000 simulations. Strategy 10 was cost-effective in 54% of the simulations. This shows that although strategy 10 is likely to be cost-effective, there is uncertainty in the results. This was highlighted by the confidence intervals around the ranking of the net monetary benefit which ranged from 1 to 4.

**Table 68: Cost-effectiveness in the base case (per patient)**

Strategy	Treatment sequence	Costs	QALYs	Cost per QALY gained (non-dominated)	NMB <sup>(a)</sup>	NMB rank (95% confidence interval) <sup>(a)</sup>	Probability of being most cost-effective strategy
10	High dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£984	0.472	£42,622 versus strategy 8	£8,454	1 (1,4)	54%
9	Low dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£1,012	0.469	Dominated	£8,364	2 (1,6)	5%
8	High dose oral ASA + beclometasone, prednisolone	£1,364	0.481	Dominated	£8,253	3 (1,7)	26%
6	Low dose oral ASA, high dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£1,013	0.461	Dominated	£8,205	4 (1,6)	12%
1	High dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£1,316	0.468	Dominated	£8,050	5 (1,6)	3%
4	Low dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£1,386	0.465	Dominated	£7,908	6 (3,7)	0%
5	Low dose oral ASA, High dose oral ASA, prednisolone	£1,509	0.459	Dominated	£7,673	7 (5,9)	0%
7	High dose oral ASA + topical ASA, prednisolone	£1,953	0.472	Dominated	£7,492	8 (3,9)	0%
2	High dose oral ASA, prednisolone	£2,144	0.463	Dominated	£7,107	9 (8,9)	0%
3	Low dose oral ASA, prednisolone	£2,345	0.458	Dominated	£6,820	10 (9,10)	0%

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

One-way sensitivity analyses were conducted in order to test the robustness of model results. Strategy 10 (high dose oral ASA followed by high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery) was the most cost effective strategy (highest NMB) across all the analyses with the exception of SA5. As strategy 8 had only two lines of treatment (one of which

was the most effective treatment choice), reducing the efficacy of non-1<sup>st</sup> line treatments had less of an effect on the NMB. Hence in SA5, it was the most cost effective strategy.

The results of the multi-variate deterministic analysis showed that the NMB decreased across all strategies as the daily costs of ASAs increased. However, strategy 10 remained the cost-effective strategy irrespective of the daily cost of ASA.

#### **5.35.4 Discussion**

##### **5.35.4.1 Limitations and interpretation**

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

##### **5.35.4.2 Generalisability to other populations/settings**

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

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

#### **5.35.5 Conclusion/evidence statement**

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

## 5.36 Clinical evidence: Immunomodulators

Four studies and one Cochrane systematic review on the use of tacrolimus were included in the review.<sup>15,103,158-160</sup> Evidence from these are summarised in the clinical GRADE evidence profiles below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

“Methotrexate for induction of remission in ulcerative colitis” was published by the Cochrane collaboration in 2007<sup>36</sup>. The review included 1 study which compared methotrexate to placebo. The Cochrane review concluded that the trial of 12.5mg of methotrexate did not show any benefit over placebo for the induction of remission in patients with active ulcerative colitis. The Cochrane review was excluded because it reported the end of trial results and the protocol for the clinical review was to include studies up to 12 weeks duration. The study was included in the clinical review but earlier results have been presented.

“Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis” was published by the Cochrane collaboration in 2008<sup>15</sup>. The review included 1 study which compared low and high trough tacrolimus to placebo. The Cochrane review has been included and updated in this clinical review.

## 5.37 Evidence profile

### 5.37.1 Immunomodulators

**Table 69: Methotrexate versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Placebo	Relative (95% CI)	Absolute		
Clinical remission -> 2≤4 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	2/30 (6.7%)	3/37 (8.1%)	RR 0.82 (0.15 to 4.61)	15 fewer per 1000 (from 69 fewer to 293 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >6≤8weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	2/30 (6.7%)	6/37 (16.2%)	RR 0.41 (0.09 to 1.89)	96 fewer per 1000 (from 148 fewer to 144 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - >8 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	6/30 (20%)	8/37 (21.6%)	RR 0.93 (0.36 to 2.37)	15 fewer per 1000 (from 138 fewer to 296 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> High drop out rate.

<sup>2</sup> Crosses the upper relative risk (RR) MID (1.25).

<sup>3</sup> Crosses the lower relative risk (RR) MID (0.75).

**Table 70: Azathioprine versus placebo (in addition to corticosteroids)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine	Placebo	Relative (95% CI)	Absolute		
Clinical remission -> 2≤4 weeks												

1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	31/40 (77.5%)	27/40 (67.5%)	RR 1.15 (0.87 to 1.51)	101 more per 1000 (from 88 fewer to 344 more)	⊕○○○ VERY LOW	CRITICAL
<b>Clinical improvement</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Endoscopic remission -&gt; 2≤4 weeks</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	15/40 (37.5%)	9/40 (22.5%)	RR 1.67 (0.83 to 3.36)	151 more per 1000 (from 38 fewer to 531 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Unclear method of randomisation. Unclear blinding.

<sup>2</sup> Include some severe ulcerative colitis patients but <10%.

<sup>3</sup> Crosses the upper 1.25 relative risk (RR) MID

**Table 71: Tacrolimus versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tacrolimus	Placebo	Relative (95% CI)	Absolute		
Clinical remission - Low trough, 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3</sup>	none	2/19 (10.5%)	1/17 (5.9%)	RR 1.79 (0.18 to 18.02)	46 more per 1000 (from 48 fewer to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission - High trough, 0≤2 weeks												
2	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	7/52 (13.5%)	1/47 (2.1%)	RR 4.43 (0.81 to 24.06)	73 more per 1000 (from 4 fewer to 491 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - Low trough, 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	8/21 (38.1%)	2/20 (10%)	RR 3.81 (0.92 to 15.81)	281 more per 1000 (from 8 fewer to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement - High trough, 0≤2 weeks												
2	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	29/51 (56.9%)	6/50 (12%)	RR 4.74 (2.16 to 10.41)	449 more per 1000 (from 139 more to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL

Endoscopic remission - Low trough, 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	8/18 (44.4%)	2/16 (12.5%)	RR 3.56 (0.88 to 14.35)	320 more per 1000 (from 15 fewer to 1000 more)	⊕○○○ VERY LOW	IMPORTANT
Endoscopic remission - High trough, 0≤2 weeks												
2	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	serious <sup>2</sup>	no serious imprecision	none	29/51 (56.9%)	6/46 (13%)	RR 4.33 (1.97 to 9.52)	434 more per 1000 (from 127 more to 1000 more)	⊕○○○ VERY LOW	IMPORTANT
Adverse events - High trough												
1	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>3</sup>	none	26/32 (81.3%)	21/30 (70%)	RR 1.16 (0.87 to 1.55)	112 more per 1000 (from 91 fewer to 385 more)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events - Low trough												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,5</sup>	none	1/22 (4.5%)	0/20 (0%)	<sup>6</sup> OR 6.75 (0.13 to 341.54)	5 more per 1000 (from 7 fewer to 17 more) <sup>7</sup>	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events - High trough												
1	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,5</sup>	none	1/21 (4.8%)	0/20 (0%)	<sup>6</sup> OR 7.05 (0.14 to 355.48)	5 more per 1000 (from 8 fewer to 17 more) <sup>7</sup>	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment.

<sup>2</sup> Indirect population (severity: moderate/severe). Some patients may have chronic active ulcerative colitis.

<sup>3</sup> 95% CI Crosses the upper 1.25 relative risk (RR) MID.

<sup>4</sup> Very limited baseline characteristics. No details on blinding of the placebo (same appearance/ taste etc.)

<sup>5</sup> 95% CI Crosses the lower 0.75 relative risk (RR) MID.

<sup>6</sup> Peto odds ratio.

<sup>7</sup> Risk difference was calculated.

**Table 72: Tacrolimus versus tacrolimus (dose comparison)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher dose	Lower dose	Relative (95% CI)	Absolute		
Clinical remission - 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	4/20 (20%)	2/19 (10.5%)	RR 1.9 (0.39 to 9.2)	95 more per 1000 (from 64 fewer to 863 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement- 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>4</sup>	none	13/19 (68.4%)	8/21 (38.1%)	RR 1.8 (0.96 to 3.36)	305 more per 1000 (from 15 fewer to 899 more)	⊕○○○ VERY LOW	CRITICAL



Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Endoscopic remission- 0≤2 weeks												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	serious <sup>4</sup>	none	15/19 (78.9%)	8/18 (44.4%)	RR 1.78 (1.01 to 3.13)	347 more per 1000 (from 4 more to 947 more)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	serious <sup>2</sup>	very serious <sup>3,4</sup>	none	1/21 (4.8%)	1/22 (4.5%)	RR 1.05 (0.07 to 15.69)	2 more per 1000 (from 42 fewer to 668 more)	⊕○○○ VERY LOW	IMPORTANT

1 Overall unclear method of randomisation and allocation concealment.  
2 Indirect population (severity: moderate/severe). Some patients may have chronic active ulcerative colitis.  
3 95% CI Crosses the lower 0.75 relative risk (RR) MID.  
4 95% CI Crosses the upper 1.25 relative risk (RR) MID.

## 5.38 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

In addition to drug costs, costs would be incurred in the due to monitoring blood levels to ensure therapeutic response. The costs of monitoring are provided in Table 73 below.

**Table 73: Cost of tests**

Type of test	Unit cost	Source
Full blood count	£3	NHS reference costs <sup>55</sup> (code DAP823)
Renal function test	£1	NHS reference costs <sup>55</sup> (code DAP841)
Liver function test	£1	NHS reference costs <sup>55</sup>
TPMT assay	£26	Crohn's guideline <sup>148</sup>

## 5.39 Evidence statements

### 5.39.1 Clinical evidence statements

#### 5.39.1.1 Methotrexate

##### Clinical remission

There may be no clinical difference between methotrexate and placebo at increasing clinical remission rates at >2≤4,> 6≤8 and >8 weeks [very low quality evidence, 1 study, N=56].

#### 5.39.1.2 Azathioprine

##### Clinical remission

Azathioprine and steroids may be more clinically effective at increasing clinical remission rates compared to placebo & steroids at >4<6 weeks [very low quality evidence, 1 study, N=80].

##### Important outcomes

Very low quality evidence showed that azathioprine & steroids may be more clinically effective at increasing endoscopic remission rates compared to placebo & steroids at >4<6 weeks [1 study, N=80].

#### 5.39.1.3 Tacrolimus

##### Clinical remission

There may be no clinically important difference in clinical remission rates between high or low trough tacrolimus compared to placebo [very low quality evidence, 2 studies, N=101, 1 study, N=41].

#### **Clinical improvement**

Both high and low trough tacrolimus may be more clinically effective at increasing clinical remission rates compared to placebo [very low quality evidence, 2 studies, N=101; 1 study, N=37].

#### **Important outcomes**

Low trough tacrolimus may be more clinically effective at increasing endoscopic remission rates compared to placebo [very low quality evidence, 1 study, N=34]. High trough tacrolimus may have a clinically higher adverse event rate compared to placebo [very low quality evidence, 1 study, N=62]. There may be no clinically important difference in serious adverse event rates between high or low trough tacrolimus compared to placebo [very low quality evidence, 1 study, N=41; 1 study, N=42].

### **5.39.1.4 Tacrolimus dose comparison**

#### **Clinical remission**

There may be no clinically important difference in clinical remission rates between high and low trough tacrolimus, the direction of the estimate of effect favoured high trough tacrolimus [Very low quality evidence, 1 study, N=39].

#### **Clinical improvement**

High trough tacrolimus may be more clinically effective at increasing clinical improvement rates compared to low trough tacrolimus, the direction of the estimate of effect favoured high trough tacrolimus [Very low quality evidence, 1 study, N=40].

#### **Important outcomes**

High trough tacrolimus may be more clinically effective at increasing endoscopic remission rates compared to low trough tacrolimus [Very low quality evidence, 1 study, N=37]. There may be no clinically important difference in serious adverse event rates between high and low trough tacrolimus [Very low quality evidence, 1 study, N=43].

### **5.39.2 Economic evidence statements**

No relevant economic evaluations were identified.

## **5.40 Recommendations and link to evidence**

<b>Recommendations</b>	<p><b>Patient information and support</b></p> <p><b>1. Discuss the disease and associated symptoms, treatment options and monitoring:</b></p> <ul style="list-style-type: none"> <li>• with the person with ulcerative colitis, and their family members or carers as appropriate and</li> <li>• within the multidisciplinary team (the composition of which should be appropriate for the age of the person) at every opportunity.</li> </ul> <p><b>Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138).</b></p>
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	<p><b>2. Discuss the possible nature, frequency and severity of side effects of drug treatment for ulcerative colitis with the person, and their family members or carers as appropriate. Refer to Medicines adherence (NICE clinical guideline 76).</b></p> <p><b>3. Give the person, and their family members or carers as appropriate, information about their risk of developing colorectal cancer and about colonoscopic surveillance, in line with the NICE clinical guidelines on:</b></p> <ul style="list-style-type: none"> <li>• <b>Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (NICE clinical guideline 118)</b></li> <li>• <b>Referral for suspected cancer (NICE clinical guideline 27)<sup>y</sup>.</b></li> </ul> <p><b>Inducing remission in people with ulcerative colitis</b></p> <p><b>Treating mild to moderate ulcerative colitis: step 1 therapy</b></p> <p><b>Proctitis and proctosigmoiditis</b></p> <p><b>4. To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis:</b></p> <ul style="list-style-type: none"> <li>• <b>offer a topical aminosalicylate<sup>z</sup> alone (suppository or enema, taking into account the person's preferences) or</b></li> <li>• <b>consider adding an oral aminosalicylate<sup>aa</sup> to a topical aminosalicylate or</b></li> <li>• <b>consider an oral aminosalicylate<sup>aa</sup> alone, taking into account the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment.</b></li> </ul> <p><b>5. To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis who cannot tolerate or who decline aminosalicylates, or in whom aminosalicylates are contraindicated:</b></p> <ul style="list-style-type: none"> <li>• <b>offer a topical corticosteroid or</b></li> <li>• <b>consider oral prednisolone<sup>bb</sup>, taking into account the person's preferences.</b></li> </ul> <p><b>6. To induce remission in people with subacute proctitis or proctosigmoiditis, consider oral prednisolone<sup>bb</sup>, taking into account the person's preferences.</b></p>
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<sup>y</sup> This guideline is being updated (publication date to be confirmed).

<sup>z</sup> At the time of publication (June 2013), 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.

<sup>aa</sup> At the time of publication (June 2013), 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.

<sup>bb</sup> Refer to the BNF for guidance on stopping oral prednisolone therapy.

	<p><b>Left-sided and extensive ulcerative colitis</b></p> <p><b>7. To induce remission in adults with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• offer a high induction dose of an oral aminosalicylate</li> <li>• consider adding a topical aminosalicylate or oral beclometasone dipropionate<sup>cc</sup>, taking into account the person's preferences.</li> </ul> <p><b>8. To induce remission in children and young people with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• offer an oral aminosalicylate<sup>dd</sup></li> <li>• consider adding a topical aminosalicylate<sup>z</sup> or oral beclometasone dipropionate<sup>ee</sup>, taking into account the person's preferences (and those of their parents or carers as appropriate).</li> </ul> <p><b>9. To induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis who cannot tolerate or who decline aminosalicylates, in whom aminosalicylates are contraindicated or who have subacute ulcerative colitis, offer oral prednisolone<sup>bb</sup>.</b></p> <p><b>Treating mild to moderate ulcerative colitis: step 2 therapy</b></p> <p><b>All extents of disease</b></p> <p><b>10. Consider adding oral prednisolone<sup>bb</sup> to aminosalicylate therapy to induce remission in people with mild to moderate ulcerative colitis if there is no improvement within 4 weeks of starting step 1 aminosalicylate therapy or if symptoms worsen despite treatment. Stop beclometasone dipropionate if adding oral prednisolone.</b></p> <p><b>11. Consider adding oral tacrolimus<sup>ff</sup> to oral prednisolone to induce remission in people with mild to moderate ulcerative colitis if there is an inadequate response to oral prednisolone after 2–4 weeks.</b></p>
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<sup>cc</sup> At the time of publication (June 2013), 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'. 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.

<sup>dd</sup> At the time of publication (June 2013), 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. Dosing requirements for children should be calculated by body weight, as described in the BNF.

<sup>ee</sup> At the time of publication (June 2013), beclometasone dipropionate 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.

	<b>12. For guidance on infliximab for treating subacute ulcerative colitis (all extents of disease), refer to Infliximab for subacute manifestations of ulcerative colitis (NICE technology appraisal guidance 140).</b>
Relative values of different outcomes	<p>The GDG considered the following outcomes direct measures that indicated recovery in patients with an acute exacerbation of ulcerative colitis:</p> <ul style="list-style-type: none"> <li>• Clinical remission (author defined)</li> <li>• Clinical improvement (author defined)</li> <li>• Quality of Life (validated indexes only)</li> </ul> <p>These were considered the critical outcomes when making decisions about the induction of remission. Clinical improvement was considered a particularly critical outcome by the patient representatives. Whilst this outcome did not indicate an absence of symptoms, a reduction of symptoms was felt to have a significant impact of a person's quality of life.</p> <p>The GDG considered the following outcomes should also be considered when making decisions on appropriate treatments for the induction of remission:</p> <ul style="list-style-type: none"> <li>• Endoscopic remission (author defined)</li> <li>• Clinical and endoscopic remission (author defined)</li> <li>• Colectomy</li> <li>• Adverse events</li> <li>• Hospitalisations</li> </ul> <p>The GDG considered endoscopic, and clinical and endoscopic remission (combined measure) as additional outcomes that may indicate recovery from an acute exacerbation of ulcerative colitis. The GDG noted that endoscopic appearances do not always correlate with clinical symptoms. There were similar problems in terms of different indexes being used to measure these outcomes and the GDG took the same approach as for clinical remission and improvement.</p>
Trade off between clinical benefits and harms	<p>The GDG recommended different treatment options for proctitis/proctosigmoiditis and left sided /extensive ulcerative colitis based on the following rationale.</p> <p><b>Proctitis/ proctosigmoiditis</b></p> <p>Recommendations 4 and 5 are underpinned by studies predominately in people with proctitis and proctosigmoiditis and showed that topical ASAs were better than placebo. On this basis an 'offer' recommendation was made.</p> <p><b>Mode of application</b></p> <p>In relation to oral versus topical ASA the evidence for method of delivery was limited and the difference in the adverse event rates between oral and topical was unclear. The GDG agreed there was clinical benefit (clinical remission, endoscopic remission and clinical improvement) for considering ASA suppositories (topical) over oral administration for people with proctitis<sup>72</sup> and hence included topical ASA application alone within the 'offer' recommendation.</p> <p>For ASA combined oral and topical administration (as opposed to either route alone) only endoscopic remission showed a slight advantage for combination therapy for people with proctosigmoiditis (this was based on one study with a &gt;50% proctosigmoiditis population)<sup>225</sup>. There was insufficient evidence to strongly recommend combined oral-topical ASA treatment. The GDG noted that oral ASAs</p>

<sup>ff</sup> At the time of publication (June 2013), tacrolimus did not have a UK marketing authorisation for this indication. 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.

demonstrated clinical benefit and were superior for inducing clinical remission and endoscopic remission compared to oral budesonide in patients with distal disease in a single study<sup>79</sup>. The GDG were concerned about the corticosteroid-related side effects and felt it was appropriate to 'consider' using combination ASA treatment before using corticosteroids. The oral drug would be given as well as the topical treatment for people who are already on ASA therapy for maintenance or based on clinical judgement according to severity of symptoms or uncertainty of disease extent.

The studies of oral ASAs were mainly in people with left sided/extensive ulcerative colitis and some excluded proctitis (or the disease extent was unknown). This meant the GDG was unable to make a strong recommendation specifically for oral ASAs in people with proctitis. Whilst the GDG were aware of the limited evidence they agreed a 'consider' recommendation for people who prefer not to use (or had difficulty administering for example older people or people with disabilities) enemas or suppositories.

In relation to recommendation 5 the evidence for people with proctitis and proctosigmoiditis is limited. Very low quality evidence from one study showed that topical steroids are better than placebo for increasing endoscopic and clinical and endoscopic remission rates in people with disease distal to the splenic flexure<sup>86</sup>. The GDG recognised that some people may be intolerant of topical ASAs or prefer a topical corticosteroid from previous treatment experience. In clinical practice, topical corticosteroids are often not step 1 therapy due to the risk of adverse events. They are sometimes used in clinical practice and the GDG acknowledged that it was important for people to have access to this treatment option despite the absence of evidence. This has been reflected in the recommendations. Likewise, the GDG also recognised that some people would prefer not to use topical treatments and so oral prednisolone could be also considered but people should be aware of systemic adverse events.

The GDG considered the use of topical steroids as a step 2 therapy for people with mild to moderate proctitis and proctosigmoiditis who have not shown any improvement within 4 weeks of starting step 1 therapy. The GDG acknowledged the absence of evidence for topical steroids for this clinical situation. Taking into account the absence of evidence and the concerns about the potential consequences of delaying treatment the GDG were unable to make a recommendation for topical steroids in this clinical context

#### **Type of preparation**

There was not enough evidence to suggest any one topical preparation (foam or liquid enema, suppository) in either an ASA or corticosteroid formulation is superior and to recommend a specific topical preparation.

#### **Children and young people**

Recommendations 4 and 5 also include children and young people. None of the studies included children or young people and the adult evidence was extrapolated. The GDG noted that topical treatments are rarely used in children and young people in the UK. From GDG experience, topical steroids can potentially be used in children with localised and distal disease, although adherence is an issue. Support and education could improve compliance of the use of topical steroids and ASAs in children and young people.

#### **Left sided/extensive**

Recommendation 7 is supported by evidence from the network meta-analysis (NMA) and these data were used in the health economic model.

The NMA showed the combination of oral mesalazine and beclometasone, oral and rectal mesalazine, balsalazide, prednisolone, high dose mesalazine were more effective than placebo at inducing clinical remission. With the exception of high dose olsalazine, the higher dose ASAs were more effective than the lower doses at inducing remission. The combination of oral mesalazine and beclometasone had the highest probability (67%) of being the best treatment followed by oral prednisolone (26%) and oral-topical mesalazine (7%).

Except for low dose sulphasalazine, all of the treatments compared in the NMA for clinical improvement had significantly better clinical improvement rates compared to placebo. The higher dose of mesalazine was significantly better for clinical improvement than the lower dose. This concurred with patient experience on the GDG. The combination of oral mesalazine and beclometasone had the highest probability (63%) of being the best treatment followed by oral-topical mesalazine (36%).

The NMA for withdrawals due to an adverse event showed that only high dose olsalazine had a significant difference in withdrawals compared to placebo. There were also significantly higher withdrawals with high dose olsalazine compared to low dose mesalazine, high dose mesalazine, balsalazide and both combination treatments (mesalazine and beclometasone, oral and rectal mesalazine). The combination of oral mesalazine and beclometasone had the highest probability (75%) of being the best treatment for the least withdrawals due to adverse events followed by balsalazide (12%) and oral-topical mesalazine (5%).

Due to the limitations of the NMAs (the evidence was mostly of very low to low quality; there was limited evidence for most of the treatments used to induce remission and the majority of the networks were made up of one study per arm, this included the combination treatments (3.2 g mesalazine (Asacol) and 5 mg beclomethasone<sup>179</sup> and 4g oral and 1g rectal mesalazine<sup>41,139</sup> and the large overlapping confidence intervals of the different treatments), it was felt that there was insufficient evidence to be confident of one treatment's superiority compared to the alternative treatment regimens for the induction of clinical remission or improvement in people with left sided or extensive ulcerative colitis compared to placebo.

The health economic model showed that a high induction dose oral ASA was always more cost-effective than a low induction dose oral ASA when used first line. The most cost-effective treatment sequence in the base case and in all the sensitivity analysis was as follows: high induction dose oral ASA followed by high induction dose oral ASA + oral beclometasone dipropionate followed by oral prednisolone.

After evaluating the evidence, clinical and patient representative experience and considering the limitations from the NMA and health economic model the GDG were confident to offer a high induction dose of an oral ASA alone in recommendation 7. The GDG were less confident in making an offer recommendation for adding beclometasone dipropionate or a rectal ASA to a high induction dose of oral ASA and they agreed a 'consider' recommendation for these treatments. In making this recommendation the GDG considered the side effect profile of steroids. Beclometasone and conventional corticosteroids (such as prednisolone) are not considered interchangeable and beclometasone has fewer side effects and as such the GDG considered they could not make a recommendation that included all steroids but one that was specific to beclometasone.

Rectal ASAs alone were not considered appropriate in people with left sided and extensive disease for the following reasons. There were limited studies with a predominantly left sided ulcerative colitis population. Furthermore, the dose and preparation of the rectal ASAs did not appear to affect clinical or endoscopic



outcomes. The GDG felt that using a topical treatment with limited local release would not be appropriate to treat extensive disease.

In relation to recommendation 9, oral ASAs may be declined, not tolerated or contraindicated in some people with ulcerative colitis and the GDG recognised some people may prefer an oral steroid despite the systemic side effects.

In clinical practice oral corticosteroids often are not first-line treatment due to the risk of adverse events associated with them but they are sometimes used in clinical practice in people with sub-acute ulcerative colitis. The GDG acknowledge it was important for this population to have access to this treatment option despite the absence of evidence. This has been reflected in recommendations 6 and 9.

### **Children and young people**

Recommendation 8 is specific to children and young people. None of the studies in the NMA included children or young people and while the adult evidence was extrapolated the GDG could not recommend a 'high' dose ASA recognising that paediatric doses should be calculated by body weight, as described in the children's BNF.

### **Mesalazine/ASA preparations**

As noted in the introduction the BNF states that: 'The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable'. In order to address this, mesalazines were compared to each other where possible and disease extent was explored where heterogeneity was present. The mesalazines were also compared to the other ASAs where possible. The direct evidence was limited and mostly of low to very low quality and did not demonstrate that any one mesalazine or an ASA preparation was clinically more effective than another. As a result the GDG were not confident in recommending one preparation over another preparation.

The oral mesalazines listed in the BNF are Asacol, Ipocol, Mesren, Mezavant, Octasa, Pentasa and Salofalk. The reviews in this guideline name the mesalazine as it is named in the studies. We are aware that the mesalazines can change brand names, for example Mesren was been rebranded as Octasa 400 in December 2012.

### **Regimen**

There was limited evidence to recommend an optimal dosing regimen. The two studies (KRUIS2009; FARUP2001) identified that assessed dosing regimens compared granules. KRUIS2009 compared once versus three times a day and FARUP2001 compared twice versus four times a day. The GDG were unable to extrapolate from the maintenance evidence as there may be differences between the two situations with regard to the optimum mucosal level of aminosalicylates and differences in transit time and luminal pH which may affect the release of 5-aminosalicylic acid.

### **Step 2 therapy – All extents of disease**

Recommendations 10 and 11 for step 2 therapy were based on indirect evidence and consensus and this is reflected in the strength of the recommendations. It was considered important to make a recommendation on treatment options if the first step therapy did not induce remission. None of the evidence for the induction of remission was in people that were clearly identified as failing first step therapy and were therefore testing a second treatment. This is problematic as when considering the efficacy of treatments for step 2 as it is based on its level of efficacy as a first treatment option. This may well over estimate a treatment's effect as a step 2 therapy.

Beclometasone is licenced for four weeks treatment so the GDG considered it was

	<p>appropriate to consider adding 40mg of prednisolone if symptoms worsened or there was no improvement within 4 weeks of step 1 therapy when beclometasone was used in combination to an oral ASA. The GDG recognised that some people are unable to be treated with oral corticosteroids (beclometasone dipropionate or prednisolone) and required another treatment option.</p> <p>Immunomodulators are considered to have greater side effects than oral corticosteroids and were considered by the GDG as the less preferred treatment option.</p> <p><b>Immunomodulators</b></p> <p>The evidence for immunomodulators was limited and of very low quality (methotrexate demonstrated no added efficacy compared to placebo, azathioprine was evaluated in combination with steroids and tacrolimus demonstrated clinical benefit compared to placebo in increasing clinical improvement rates).</p> <p>After considering the clinical evidence, the GDG recommended the use of tacrolimus for people that cannot be treated with oral corticosteroids (recommendation 11). The GDG decided to recommend tacrolimus over the use of other immunomodulators for the following reasons:</p> <ul style="list-style-type: none"> <li>• The lack of evidence to support the use of methotrexate (however it was noted the dose used in the trial was lower than is used in current clinical practice)<sup>160</sup>. The GDG acknowledged that there may be a role for a higher dose of methotrexate for patients who are refractory to other treatments based on their experience.</li> <li>• The GDG felt that azathioprine takes too long to have an effect and its role is limited for induction of remission.</li> <li>• In people who have not responded to prednisolone, the GDG noted benefit of tacrolimus<sup>158,159</sup>.</li> </ul> <p>The GDG recognised there is limited evidence on tacrolimus as a long term treatment or as a bridge to another treatment. The two studies<sup>158,159</sup> showing benefit of tacrolimus were of 12 weeks duration (2 week RCT followed by a 10 week open label extension). As a result the GDG were unable to comment on the length of time tacrolimus should be used for and noted that nephrotoxicity and opportunistic infections may be an issue with longer term use and recommended regular monitoring (recommendation 18). Nephrotoxicity (increase by &gt;30% of baseline creatinine level) occurred in 14.8% of participants followed up at 12 weeks (2 week trial followed by a 10 week open label extension)<sup>158</sup>. Monitoring for toxicity including renal dysfunction, low magnesium and infection was considered essential by the GDG.</p> <p><b>Prednisolone</b></p> <p>The GDG felt it was important to note that an appropriate starting dose for oral prednisolone in adults should be 40mg per day. This was supported by Baron<sup>13</sup> which showed that 40mg per day was more effective than 20mg per day and as effective as 60 mg per day for clinical improvement and clinical and endoscopic remission. For children and young people please refer to the BNF for children.</p>
Economic considerations	<p><b>Proctitis/ proctosigmoiditis</b></p> <p>No cost-effectiveness evidence was identified. The costs of topical aminosalicylates and steroids are dependent on the formulation and the daily dose administered. However, it is possible that cost savings could be made if a suppository is used over an enema. The use of ASA suppositories rather than oral ASAs is likely to be cost-effective because the clinical effectiveness data shows clinical benefit and the average cost is lower than oral ASA.</p>

	<p><b>Left sided and extensive</b></p> <p>A systematic literature search identified four relevant studies evaluating the cost-effectiveness of drugs for the induction of remission. A study by Brereton<sup>25</sup> found 2.4g/day Mezavant XL to be more expensive and effective than 2.4g/day Asacol with an incremental cost-effectiveness ratio of £749 per QALY. A study by Buckland<sup>26</sup> which compared 4.8/day to 2.4g/day Asacol found the higher dose to be cost-effective. 6.75g Balsalazide was compared to 2.4g or 4.8g/day Asacol by Mackowiak<sup>132</sup>. Balsalazide was shown to be the cost-effective option. Combination treatment of oral and topical mesalazine was found to be cost-effective compared with oral mesalazine alone by Connolly<sup>39</sup>.</p> <p>The results of these studies were reviewed by the GDG. It was however noted that other treatment options not included in the cost-effectiveness studies were available. Because the studies only helped to highlight the cost-effectiveness of some treatments and because this is an area of uncertainty, the GDG considered it a high priority for original economic analysis. Based on this, a decision-analytic model was developed with a 28-week time horizon. It addressed the use of various sequences of drugs as chosen by the GDG for induction of remission.</p> <p>The model showed that a high induction dose oral ASA was always more cost-effective than a low induction dose oral ASA when used first line.</p> <p>As noted above, the cost-effective treatment sequence in the base case and in six sensitivity analysis was as follows: high induction dose oral ASA followed by high induction dose oral ASA + oral beclometasone dipropionate followed by oral prednisolone.</p> <p>In interpreting the results, limitations of the model as highlighted below needed to be considered:</p> <ul style="list-style-type: none"> <li>• The costs and dis-utilities of drug-specific adverse events were not captured in the model due to lack of robust data. This means that the cost-effectiveness of all the treatments strategies has been over-estimated although the magnitude is unknown as each drug is likely to have a different, specific side-effect profile. This introduces uncertainty around interpretation of the results.</li> <li>• The clinical data informing the treatments that were not first line were obtained from studies that had trialled the drugs as first line. This meant that the effectiveness may have been over-estimated when used as non-first line treatments. Consequently, this would impact on the cost-effectiveness of the overall strategy. A sensitivity analysis was conducted to address this issue. All the treatment strategies compared became less cost-effective however the most cost-effective option was still the same as the base case.</li> <li>• Patients who fail the final course of ASA therapy in each treatment sequence are switched to prednisolone. The GDG noted that in clinical practice patients, prednisolone could be added on to existing ASA therapy. However this could not be modelled due to lack of clinical data for the use of combination treatment with ASA and prednisolone. The GDG acknowledged the analysis might underestimate the side effects and costs of combination therapy.</li> </ul> <p><b>Immunomodulators</b></p> <p>No cost-effectiveness evidence was identified. The GDG considered the costs of tacrolimus and also noted that drug monitoring would be required. It was felt that due to the level of disease severity in this sub group of patients, these costs are likely to be offset by the potential benefits. Benefits would include avoidance of escalation to intravenous therapy and reduced hospitalisations.</p>
Quality of evidence	<p>The majority of the evidence for the outcomes for proctitis and proctosigmoiditis was of low to very low quality and consisted of some mixed populations. There were a limited number of studies. There was no evidence for oral versus rectal steroids.</p>

	<p>The majority of the evidence for the outcomes for left sided and extensive disease was of low to very low quality. The GDG noted that there was evidence identified about the following oral aminosaliclates: Sulphasalazine, balsalazide, olsalazine and mesalazine (the brand names of the mesalazines in the published papers were Asacol, Pentasa, Mezavant XL and Ipocol). Mesren or Octasa were not named in the papers.</p> <p>The NMA was based on a total of 25 studies of 10 different interventions (7 mono-therapies, 2 combination therapies). The majority of the evidence for the outcomes had a rating of low to very low quality. For more detail see the limitations listed above for the NMA and health economic model.</p> <p>There were very few studies looking at the use of immunomodulators whose outcomes were all very low quality. There was no evidence for the use of mercaptopurine.</p> <p>There were no studies which enabled hazard ratio data to be extracted, so all of the analysis was based on relative risks at different time points during the studies. The impact of extent of disease was difficult to evaluate as the majority of the studies evaluating oral treatments had mixed extent populations and the studies evaluating topical treatments had a majority proctitis/ proctosigmoiditis populations.</p>
Other considerations	<p>The GDG has listed the high induction doses of all the aminosaliclates. The GDG defined high induction doses as: more than 2.4g for mesalazine; more than 6g for sulphasalazine; more than or equal to 1.5g for olsalazine. There is only one dose for balsalazide, 6.75g. The GDG definition was based on the ranges of doses in the drugs' summary of product characteristics and the dose comparisons used in the clinical evidence reviews.</p> <p>The NMA demonstrated that sulphasalazine was less effective than placebo. This was thought to be due to the low quality of the sulphasalazine study. Sulphasalazine is an ASA which is available in liquid preparation and may be useful for children and young people who are unable to swallow tablets. Sulphasalazine may provide an alternative to escalating treatment prematurely to steroid use.</p> <p>As noted above in the 'trade off between benefits and harms' there was very limited evidence to recommend one preparation over another or once daily compared to conventional dosing.</p> <p>The GDG patient representatives felt that patient preference might tend towards suppositories as opposed to enemas for the topical preparations (easier to control the dose) and two doses per day was not practical for patients.</p> <p>GDG were surprised by the lack of evidence for the use of steroids as there is considerable clinical experience in inducing remission in people with ulcerative colitis. The GDG discussed whether beclometasone might be considered alone for people who are unable to tolerate an aminosaliclate but this would be outside its licence and has limited evidence and clinical experience. The GDG were unable to make any recommendation about beclometasone as a monotherapy.</p> <p><b>Research recommendations</b></p> <p>The GDG agreed that the lack of evidence for the induction of remission in people with ulcerative colitis justified developing research recommendations to address whether these treatments are effective. For further information on the research recommendations see Appendix M.</p>

## **5.41 Review question: In adults, children and young people with acute severe ulcerative colitis, what is the clinical and cost-effectiveness of corticosteroids and ciclosporin compared to each other and their combination (corticosteroids and ciclosporin) for the induction of remission?**

For full details see review protocol in Appendix C.

## **5.42 Clinical evidence: Acute severe ulcerative colitis**

The literature search identified four RCTs<sup>23,51,126,223</sup> comparing corticosteroids and/or ciclosporin with corticosteroids and/or corticosteroids and/or placebo that met the inclusion criteria.

There were no limitations on sample size and only direct studies relating to the patient disease severity were included. No indirect interventions, comparisons or outcomes were considered. Only randomised controlled trials were included. Phase I, non randomised Phase II trials and cross over trials were excluded. Abstracts were not included unless there were no randomised controlled trial full papers for the comparison.

An author defined definition of the clinical, endoscopic and clinical and endoscopic remission and clinical improvement was used due to the extensive numbers of different indexes used by the authors. Many of these are unvalidated and it carries a high risk of bias however, by choosing one index it was felt that too many studies would be excluded and there would be a lack of evidence to consider. Therefore, the bias associated with using the author's definitions was taken into account when analysing the data.

There were no setting restrictions. A trial duration limit of 4 weeks was applied.

The following subgroups were considered for subgroup analysis in the event of heterogeneity in the meta-analysis:

- Age (adults, children and young people)

Where possible, the evidence was analysed by meta-analysis and GRADE, and these results are presented in a GRADE profile. Where studies reported data which could not be analysed by meta-analysis or GRADE, a narrative summary is provide below the GRADE profiles.

"Cyclosporine A for induction of remission in severe ulcerative colitis" was published by the Cochrane collaboration in 2005 and was updated in 2008<sup>200</sup>. No additional studies were identified in the update. The review included 2 studies which compared ciclosporin to placebo/steroids. The Cochrane review concluded that the evidence was limited that cyclosporine was more effective than standard treatment alone for severe ulcerative colitis. The long term benefit is unclear in terms of adverse event risk. The Cochrane review was excluded as it did not quite fit our protocol; an acute episode of severe ulcerative colitis was not specified, did not include a child and young person population or ciclosporin and IV corticosteroid dose comparisons, and the outcome definition was different (outcome in the Cochrane review; no induction of remission which included those that did not improve, outcomes in the clinical review; clinical remission and clinical improvement analysed separately). Both of the studies identified in the Cochrane review were included in our review.

## 5.43 Evidence profile

### 5.43.1 IV ciclosporin and steroids versus placebo and steroids

Table 74: IV ciclosporin and steroids versus placebo and steroids

Quality assessment							No of patients		Effect		Quality	Importanc e
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ciclosporin and steroids	Placebo and steroids	Relative (95% CI)	Absolute		
Colectomy (0≤2 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/11 (27.3%)	4/9 (44.4%)	RR 0.61 (0.18 to 2.06)	173 fewer per 1000 (from 364 fewer to 471 more)	⊕○○○ VERY LOW	CRITICAL
Mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement (0≤2 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/11 (81.8%)	0/9 (0%)	OR <sup>3</sup> 23.12 (4.11 to 129.85)	820 more per 1000 (from 550 fewer to 1000 more)	⊕⊕⊕○ MODERAT E	CRITICAL
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Unclear randomisation and allocation concealment

<sup>2</sup> 95% CI crosses the upper (1.25) and lower (0.75) relative risk (RR) MIDs.

<sup>3</sup> Peto odds ratio

<sup>4</sup> Risk difference measured

#### Additional narrative information which could not be meta-analysed:

There was no data on the number of patients experiencing one or more adverse events reported in the study. Adverse events which were reported in the two treatment arms were:

- Ciclosporin: Parasthesias 4/11, hypertension 4/11 (2 requiring treatment), nausea and vomiting 1/11, grand mal seizure 1/11
- Placebo: Hypertension 1/9, nausea and vomiting 1/9

Mortality was also reported but it was unclear at how many weeks this occurred. On patient in the placebo group had a colectomy due to clinical deterioration and they later died of gram negative sepsis with superimposed cytomegalovirus infection.

**Table 75: IV ciclosporin versus IV steroids**

Quality assessment							No of patients		Effect		Quality	Importanc e
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV ciclosporin	IV steroids	Relative (95% CI)	Absolute		
Colectomy (0≤2 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	2/14 (14.3%)	0/15 (0%)	OR <sup>3</sup> 8.57 (0.51 to 144.39)	140 more per 1000 (from 60 fewer to 350 more) <sup>4</sup>	⊕○○○ VERY LOW	CRITICAL
Mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement (0≤2 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	9/14 (64.3%)	8/15 (53.3%)	RR 1.21 (0.65 to 2.23)	112 more per 1000 (from 187 fewer to 656 more)	⊕○○○ VERY LOW	CRITICAL
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Unclear method of randomisation

<sup>2</sup> The 95%CI crosses the lower (0.75) and upper (1.25) relative risk (RR) MID

<sup>3</sup> Peto odds ratio

<sup>4</sup> Risk difference measured

**Additional information which could not be meta-analysed:**

There was no data on the number of patients experiencing one or more adverse events reported in the study. Adverse events which were reported in the two treatment arms were:

- Ciclosporin: Hypertension 1/11, superficial thrombophlebitis 1/11, headache 2/11, vomiting 1/11, epigastric discomfort 0/11, hypokalemia 4/22, hypomagnesia 2/11, myalgia 2/11. Side effects beyond the first week of treatment but stopped when the ciclosporin was discontinued were; gingival hyperplasia (3), hypertension (1), tremor (1), hair loss (1) and headache (1).
- Steroids: Superficial thrombophlebitis 1/15, headache 1/15, epigastric discomfort 1/15, parasthesia 1/15, myalgia 1/15

**Table 76: 4 mg/kg ciclosporin versus 2 mg/kg ciclosporin**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4 mg/kg ciclosporin	2 mg/kg ciclosporin	Relative (95% CI)	Absolute		
Colectomy												
0	No evidence available					none	-	-	-	-		CRITICAL
Mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical improvement (0≤2 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/38 (84.2%)	30/35 (85.7%)	RR 0.98 (0.81 to 1.19)	17 fewer per 1000 (from 163 fewer to 163 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical remission												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Unclear method of randomisation

**Additional information which could not be meta-analysed:**

There was no data on the number of patients experiencing one or more adverse events reported in the study. Adverse events which were reported in the two treatment arms were:



- 4 mg/kg: Neurological 3/38, novel cases of hypertension 9/38, increase serum creatinine (> 10%) 7/38, fever 3/38, diabetes mellitus 1/38, anaphylactic reaction 1/38
- 2 mg/kg: Neurological 2/35, novel cases of hypertension 3/35, increase serum creatinine (> 10%) 6/35, fever 1/35, diabetes mellitus 0/35

**Table 77: IV steroids (infusion) versus IV steroids (bolus)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV steroids (infusion)	IV steroids (bolus)	Relative (95% CI)	Absolute		
Colectomy (>2≤4 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	5/34 (14.7%)	5/32 (15.6%)	RR 0.94 (0.3 to 2.95)	9 fewer per 1000 (from 109 fewer to 305 more)	⊕○○○ VERY LOW	CRITICAL
Clinical improvement												
0	No evidence available					none	-	-	-	-		CRITICAL
Mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
Clinical remission (0≤2 weeks)												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	17/34 (50%)	16/32 (50%)	RR 1 (0.62 to 1.62)	0 fewer per 1000 (from 190 fewer to 310 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	13/34 (38.2%)	15/32 (46.9%)	RR 0.82 (0.46 to 1.43)	84 fewer per 1000 (from 253 fewer to 202 more)	⊕○○○ VERY LOW	IMPORTANT

- <sup>1</sup> Unclear allocation concealment
- <sup>2</sup> The 95%CI crosses the lower (0.75) and upper (1.25) relative risk (RR) MID

## 5.44 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 5.45 Evidence statements

### 5.45.1 Clinical evidence statements

#### 5.45.1.1 IV ciclosporin & IV steroids versus IV placebo & IV steroids

##### Clinical improvement

IV ciclosporin plus IV steroids is more clinically effective at increasing clinical improvement rates at 0≤2 weeks compared to IV placebo plus IV steroids [Very low quality evidence, 1 study, N=20].

##### Important outcome

IV ciclosporin plus IV steroids may be more clinically effective at reducing colectomy rates at 0≤2 weeks compared to IV placebo plus IV steroids [Very low quality evidence, 1 study, N=20].

#### 5.45.1.2 IV ciclosporin versus IV steroids

##### Clinical improvement

IV ciclosporin may be more clinically effective at increasing clinical improvement rates at 0≤2 weeks compared to IV steroids [Very low quality evidence 1 study, N=29].

##### Important outcome

IV steroids may be more clinically effective at decreasing colectomy rates at 0≤2 weeks compared to IV ciclosporin [Very low quality evidence 1 study, N=29].

#### 5.45.1.3 Ciclosporin dose comparison

##### Clinical improvement

There is no clinically important difference between 4mg/kg versus 2mg/kg ciclosporin in clinical remission rates at 0≤2 weeks [moderate quality evidence, 1 study, N=73].

#### 5.45.1.4 Corticosteroid preparation

##### Clinical remission

There may be no clinically important difference between iv steroids (infusion) and iv steroids (bolus) in clinical remission rates at 0≤2 weeks [very low quality evidence 1 study, N=66].

### Important outcomes

There may be no clinically important difference between iv steroids (infusion) and iv steroids (bolus) in colectomy rates at >2≤4 weeks [very low quality evidence 1 study, N=66]. There may be no clinically important difference between iv steroids (infusion) and iv steroids (bolus) in adverse event rates [very low quality evidence 1 study, N=66].

## 5.45.2 Economic evidence statements

No relevant economic evaluations were identified.

## 5.46 Recommendations and link to evidence

<b>Recommendations</b>	<p><b>Treating acute severe ulcerative colitis: all extents of disease</b></p> <p><b>The multidisciplinary team</b></p> <p><b>13.For people admitted to hospital with acute severe ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• ensure that a gastroenterologist and a colorectal surgeon collaborate to provide treatment and management</li> <li>• ensure that the composition of the multidisciplinary team is appropriate for the age of the person</li> <li>• seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person</li> <li>• ensure that the obstetric and gynaecology team is included when treating a pregnant woman.</li> </ul> <p><b>Step 1 therapy</b></p> <p><b>14.For people admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation):</b></p> <ul style="list-style-type: none"> <li>• offer intravenous corticosteroids to induce remission and</li> <li>• assess the likelihood that the person will need surgery (see recommendation 19).</li> </ul> <p><b>15.Consider intravenous ciclosporin<sup>gg</sup> or surgery for people:</b></p> <ul style="list-style-type: none"> <li>• who cannot tolerate or who decline intravenous corticosteroids or</li> <li>• for whom treatment with intravenous corticosteroids is contraindicated.</li> </ul> <p><b>Take into account the person's preferences when choosing treatment.</b></p> <p><b>Step 2 therapy</b></p> <p><b>16.Consider adding intravenous ciclosporin<sup>gg</sup> to intravenous corticosteroids or consider surgery for people:</b></p>

<sup>gg</sup> At the time of publication (June 2013), ciclosporin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent

	<ul style="list-style-type: none"> <li>• <b>who have little or no improvement within 72 hours of starting intravenous corticosteroids or</b></li> <li>• <b>whose symptoms worsen at any time despite corticosteroid treatment.</b></li> </ul> <p><b>Take into account the person's preferences when choosing treatment.</b></p> <p><b>17.For guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to Infliximab for acute exacerbations of ulcerative colitis (NICE technology appraisal guidance 163).</b></p> <p><b>Monitoring treatment</b></p> <p><b>18.Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring (aminosalicylates, tacrolimus, ciclosporin, infliximab, azathioprine and mercaptopurine). Nominate a member of staff to act on abnormal results and communicate with GPs and people with ulcerative colitis (and/or their parents or carers as appropriate).</b></p>
Relative values of different outcomes	<p>The GDG considered the following outcomes direct measures that indicated recovery in patients with an acute severe exacerbation of ulcerative colitis:</p> <ul style="list-style-type: none"> <li>• Colectomy</li> <li>• Mortality</li> <li>• Clinical improvement (author defined)</li> <li>• Clinical remission (author defined)</li> <li>• Quality of Life (validated indexes only)</li> </ul> <p>These were considered the critical outcomes in making decisions about the induction of remission. Clinical improvement was considered a particularly critical outcome by the patient representatives. While this outcome did not indicate an absence of symptoms a reduction of symptoms was felt to have a significant impact of a person's quality of life.</p> <p>The GDG considered the following outcomes should also be considered when making decisions on appropriate treatments for the induction of remission:</p> <ul style="list-style-type: none"> <li>• Endoscopic remission</li> <li>• Clinical and endoscopic remission</li> <li>• Adverse events</li> </ul> <p>The GDG considered endoscopic, and clinical and endoscopic remission (combined measure) as additional outcomes that may indicate recovery from an acute exacerbation of ulcerative colitis. Endoscopic appearances do not always correlate with clinical symptoms. There were similar problems in terms of different indexes being used to measure endoscopic, and clinical and endoscopic remission (combined measure) and the GDG took the same approach as for clinical remission and</p>

should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

	improvement.
Trade off between clinical benefits and harms	<p>The limited clinical evidence demonstrated that intravenous ciclosporin alone or with intravenous corticosteroids was more effective than intravenous corticosteroids alone in increasing clinical improvement rates. The evidence for the reduction of colectomy rates was contradictory: intravenous ciclosporin plus intravenous steroids may be more effective at reducing colectomy rates than intravenous steroids plus placebo<sup>126</sup> whereas DHAENS2001<sup>51</sup> found intravenous steroids may be more clinically effective at decreasing colectomy rates at 0–2 weeks compared to intravenous ciclosporin. No clinical difference was demonstrated in ciclosporin doses for clinical improvement rates.</p> <p>The GDG discussed the needs of people with acute severe ulcerative colitis and the importance of balancing the risks of continued medical treatment with surgery. This focused on the adverse events associated with intravenous steroids and, in particular, immunosuppression associated with ciclosporin. Based on clinical experience, taking into account adverse events and costs, the GDG recommended that intravenous corticosteroids should be offered first and the need for surgery should be assessed. Intravenous ciclosporin or infliximab should be considered in specific circumstances (refer to NICE Technology Appraisal 163).</p> <p>The choice between ciclosporin and surgery requires careful clinical judgement that takes into account the person's clinical condition, time since initiation of intravenous steroids and acknowledges the importance of avoiding unnecessary delays in considering surgery. Time to response to ciclosporin or infliximab should be taken into account in decision-making.</p>
Economic considerations	No cost-effectiveness evidence was identified. The GDG considered that for this population, drug treatment would be necessary, due to risk of mortality if left untreated. Hence the costs attributed to treatment would be offset by the potential benefits to patients in terms of improvement of symptoms, possible avoidance of surgery and reduction in mortality.
Quality of evidence	<p>There was limited evidence for the outcomes. Mortality, clinical improvement and quality of life were not reported in any study, clinical remission was reported in one study, colectomy in three studies and adverse events in one study. The evidence was mostly of very low quality and came from four studies with small sample sizes.</p> <p>There were no studies which enabled hazard ratio data to be extracted, so all of the analysis was based on relative risks at different time points during the studies.</p>
Other considerations	<p>Although the evidence is limited, there are no other treatment options for people with acute severe colitis on admission to hospital. The GDG acknowledge that these are strong recommendations based on weak evidence, but since there are no other treatment options for acute severe attacks and high mortality rates<sup>73</sup> where acute severe ulcerative colitis is untreated, the GDG felt it was appropriate to make these recommendations.</p> <p>The GDG noted there are two clinical trials awaiting publication (GETAID CYSIF study and CONSTRUCT) that compare infliximab and ciclosporin. The GETAID CYSIF study reported at the 6th Congress of the European Crohn's and Colitis Organisation in February 2011. These trials will aid further decision-making on treatment options for</p>

this population.

The GDG noted the importance of using heparin or low-molecular weight heparin in patients being treated with severe ulcerative colitis. NICE clinical guideline 92 'Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital' refers to inflammatory conditions as a risk factor for venous thromboembolism in combination with the expectation of ongoing reduced mobility relative to their normal state while in hospital.

## 5.47 Clinical introduction: Assessing likelihood of needing surgery

Patients with ulcerative colitis may need a colectomy to control acute severe disease, chronic active disease (with poor quality of life) or to treat cancer or pre-cancerous changes. The timing of surgery in acute colitis is difficult, particularly during an acute attack when surgery carries a much greater risk of complications. The aim is to strike a balance between risking the most serious complications of colonic perforation or severe bleeding on the one hand and operating too early when medical therapy might have induced a remission. The timing of surgery (open or laparoscopic) should be when a patient is relatively healthy and can withstand a major abdominal operation and go on to a quick uneventful recovery. This aim has to be balanced against the avoidance of an operation that may mean the formation of an ileostomy, which may for some, be permanent. While ultimately a stoma can provide good quality of life, patients and their relatives may perceive having an ileostomy as a severe limitation with associated implications for their body image. For the majority, now, most patients can have reconstructive surgery and have the ileostomy closed following construction of an ileo-anal pouch. This will require an additional operation and also in some, a further procedure to close a loop ileostomy. Following colectomy, it is important that the rectum is not left in-situ. Firstly, many patients have symptoms from defunctioned proctitis that can be troublesome for a proportion. Secondly, the defunctioned rectum poses a cancer risk and surveillance is difficult. Patients who wish to avoid further operations may request a one-stage procto-colectomy. This may be acceptable in the elective setting, but in urgent cases is associated with a much greater degree of morbidity (complications). Moreover, an acute attack is not a good time for making irreversible decisions that might be regretted when the patient has regained their health. Once the anus has been removed, clearly the option of reconstructive surgery has been lost. The Cleveland Clinic data suggests that complications from reconstructive surgery and pouch failure are reduced if reconstructive surgery is delayed for a minimum of 6 months following the colectomy.

### Acute attack

Traditionally the timing of surgery is based upon signs of a severe illness (including fever, tachycardia, hypotension and anaemia). The classical data is retrospective and relates to patients who have had a colectomy. This report examines the data available about patients who have had a colectomy and tries to determine the factors that make a colectomy a likely outcome.

## 5.48 Review question: Which validated tools are the most predictive of the likelihood of surgery in people with acute severe ulcerative colitis?

For full details see review protocol in Appendix C.

## 5.49 Clinical evidence: Timing of surgery

7 studies were included in the review.<sup>1,14,98,128,198,214,217</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots and ROC curves in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

One systematic review was identified,<sup>211</sup> and used to cross check the included indexes and their references. It was not included in this review as there was insufficient detail on the indexes and the focus of the systematic review was not solely validated indexes but included clinical parameter and biomarker associations.

Four indices were identified that were developed to predict the colectomy rates associated with acute severe ulcerative colitis; Ho index, Travis index (Oxford Index), Seo index and the Lindgren index (FCI, Fulminant Colitis Index). See Table 78 for a summary of the indices.

**Table 78: Summary of the indices used in the studies**

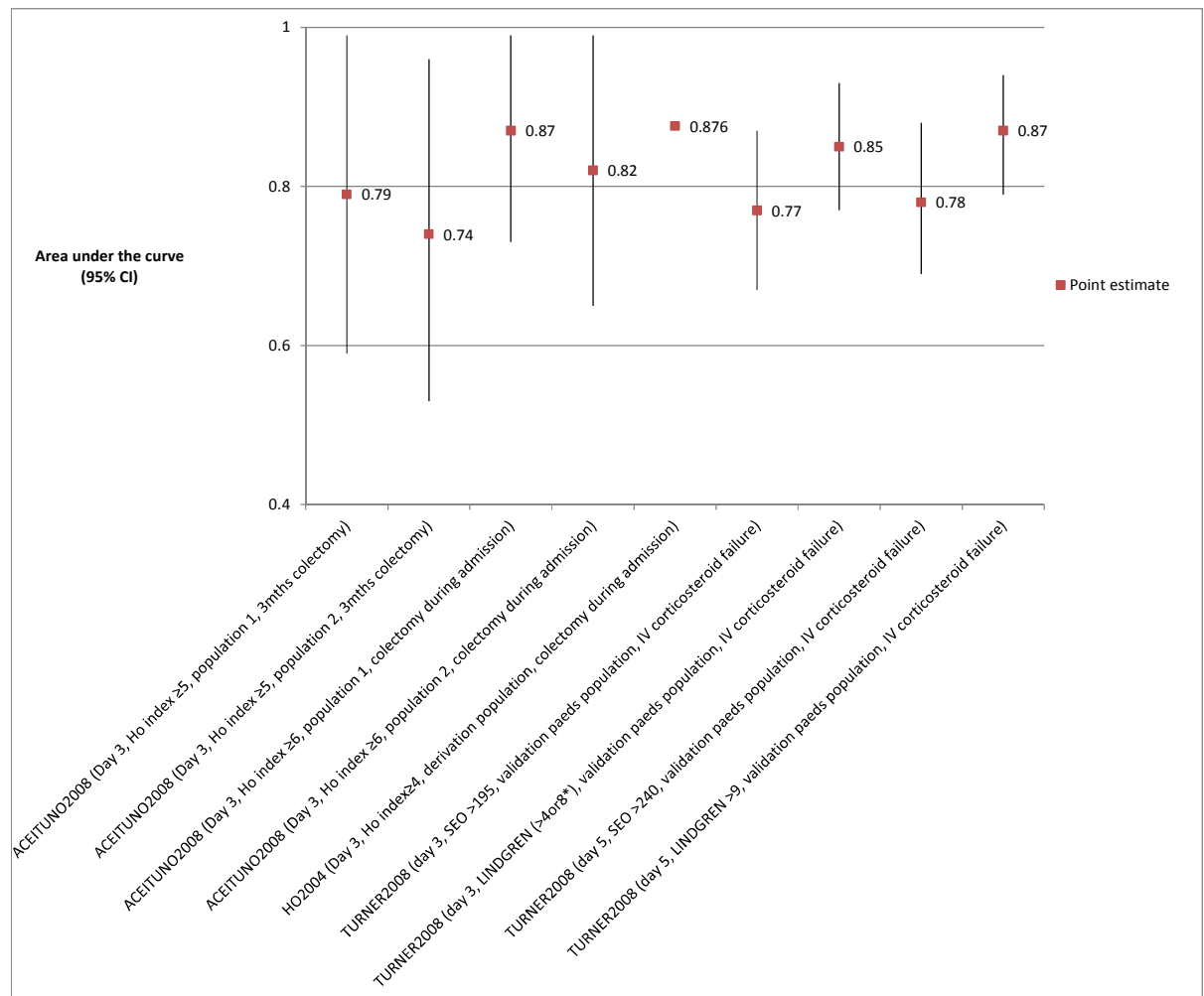
Name of Index	Components/ risk score	Cut offs reviewed
Ho index	Mean stool frequency <4 – score 0 Mean stool frequency >4≤6 – score 1 Mean stool frequency >6≤8 – score 2 Mean stool frequency >9 – score 4 Colonic dilatation – score 4 Hypoalbuminaemia (<30g/l) – score 1	Day 3 total score ≥4 Day 3 total score ≥5 Day 3 total score ≥6
Lindgren (FCI) index	Number of bowel movements +0.14 x CRP	Day 3 score>4 Day 3 score >8 Day 5 score >9
Seo Index (AI-activity index)	(60 x bloody stools) + (0.5 x ESR) + (13 x bowel movements) – (4xHb) – (15 x albumin) +200	Pre-treatment >210 Day 3 >195 Day 5 >240 1 week >180 2 weeks >180, >190, >200, >210
Travis index	>8 bowel actions on day 3, or with 3-8 bowel actions and a CRP>45mg/l	N/A

Indices were only included if they had been validated, either internally or externally. Some of the older indexes did not include validation in the original studies; Travis index (TRAVIS1996), Ho index (HO2004), Lindgren (FCI) index (LINDGREN1998) and Seo index (SEO2002). The validation was done in additional studies carried out. The paediatric index (PUCAI) did not have a derivation study and was only reported in the TURNER2008 paper when compared to other indexes. Therefore this index has been excluded.

No studies carried out internal validation but 3 studies had an external validation of the indexes. None of the studies reported calibration data.

### 5.49.1 Summary of results for AUC

**Figure 4: Included studies area under the curve and 95% CI**





## 5.50 Evidence profile

### 5.50.1 Risk assessment of the validation of the indexes

**Table 79: Risk assessment of the validation of the indexes**

Study characteristics			Quality assessment					Summary of findings			
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95%CI)	Quality
ACEITUNO2008 Day 3 Ho index ≥5	Prospective cohort, prospectively collected from established databases in 2 Spanish university hospitals.  Colectomy in first 3 months.	External validation population 1: n=34	Very serious <sup>hh</sup>	None	None	Not applicable	Steroid refractory	0.55 (0.23, 0.83) <sup>ii</sup>	0.91 (0.72, 0.99)	0.79 (0.59, 0.99)	Low
		External validation population 2: n=38	Very serious <sup>a</sup>	None	None	Not applicable	Steroid refractory (ciclosporin treated)	0.56 (0.21, 0.86)	0.83 (0.64, 0.94)	0.74(0.53, 0.96)	Low

- hh Both external validations have been carried out by the same authors. <100 events, small sample size. Unclear how accurate the databases record the colectomy outcome. Colectomy is not from the hospital admission, it is up to 3 months. Partially inadequate event: covariate ratio (3-6).
- ii The figures given in the paper were sensitivity 55%, specificity 91%, PPV 66.6%, NPV 80%. When calculated the figures do not add up/ there must be an error in the reporting. The figures given in the table have been calculated so that the figures add up for sensitivity and specificity.

Study characteristics			Quality assessment					Summary of findings			
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95%CI)	Quality
	Exploratory analysis: <b>Only colectomies during admission</b>	External validation population 1: n=34	Very serious <sup>jj</sup>	None	None	Not applicable	Steroid refractory	Not reported/able to be calculated	Not reported/able to be calculated	0.87 (0.73, 0.99)	Low
		External validation population 2: n=38	Very serious <sup>c</sup>	None	None	Not applicable	Steroid refractory	Not reported/able to be calculated	Not reported/able to be calculated	0.82 (0.65, 0.99)	Low
BAUDET2010  <b>Day 3</b>  <b>FCI (Lindgren Index)</b>	Retrospective cohort, retrieved medical files <b>Infliximab population</b>  <b>Colectomy up to 30 weeks (median 6, range 4-30)</b>	Validation: n=43 FCI≥8 FCI≥10 FCI≥12 FCI≥14 FCI≥16	Very serious <sup>kk</sup>	None	None	Not applicable	Infliximab population	1.00 (0.63, 1.00) 0.75 (0.35, 0.97) 0.75 (0.35, 0.97) 0.63 (0.24, 0.91) 0.50 (0.16, 0.84)	0.20 (0.08, 0.37) 0.37 (0.21, 0.55) 0.57 (0.39, 0.74) 0.69 (0.51, 0.83) 0.86(0.70, 0.95)	Not reported/able to be calculated	Low

jj Both external validations have been carried out by the same authors. <100 events, small sample size. Unclear how accurate the databases record the colectomy outcome. Inadequate event: covariate ratio (0-2).

kk Retrospective cohort, event rate <100, unclear missing data, partially inadequate event: covariate ratio (3-6).

Study characteristics			Quality assessment					Summary of findings			
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95%CI)	Quality
TURNER2008	Retrospective cohort, electronic database and ICD coding External validation	Validation: n=99 <b>Day 3</b> Lindgren (>4) Seo (>195) Lindgren (>8) Travis <b>Day 5</b> Lindgren (>9) Seo (>240) Travis	Very serious <sup>II</sup>	None	Outcome was failed steroids. 4 patients in this group did not have a colectomy (<10%)	Not applicable		0.91 (0.79, 0.98)	0.57 (0.42, 0.70)	0.85(0.77,0.93)*	Low
<b>Day 3 and 5</b>								0.91 (0.79, 0.98)	0.43 (0.30, 0.58)	0.77 (0.67, 0.87)	
<b>Travis Index</b>								0.63 (0.48, 0.77)	0.92 (0.82, 0.98)	0.85(0.77,0.93)*	
<b>Lindgren Index (FCI)</b>								0.37 (0.23, 0.52)	1.00 (0.93, 1.00)	-	
<b>Seo Index</b>								0.37 (0.23, 0.52)	0.98 (0.90, 1.00)	0.87 (0.79, 0.94)	
<b>PUCAI</b>								0.26 (0.14, 0.41)	0.92 (0.82, 0.98)	0.78 (0.69, 0.88)	
	<b>Paediatric population</b>							0.22 (0.11, 0.36)	1.00 (0.93, 1.00)	-	
	<b>Colectomy (or second line treatment) during hospitalisation</b>										

(a) \*it is unclear from the paper whether the AUROC for the Lindgren Index on Day 3 refers to the >4 or >8 cut off.

**Note:** Where the true positive, true negative, false positive and false negative data has not been reported in the paper, the sensitivity and specificity data has been used in order to calculate it. The sensitivity and specificity data reported in the table above may slightly differ from that reported in the papers due to using the figures estimated for the TP/ TN/ FP/ FN.

II Retrospective cohort, risk of inaccurate ICD coding, unclear if missing data, event rate <100.

## 5.51 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

## 5.52 Evidence summary

### 5.52.1 Clinical evidence summary

The quality of the validation of the four identified was graded as low. The AUC reported in the studies ranged from 0.74 to 0.87 indicating a range from a moderate to good ability to predict the likelihood of needing surgery. All the confidence intervals overlapped making it difficult to identify one index as superior to the others.

### 5.52.2 Economic evidence summary

No relevant cost-effectiveness evidence was identified.

## 5.53 Recommendations and link to evidence

Recommendations	<p><b>Assessing likelihood of needing surgery</b></p> <p><b>19. Assess and document on admission, and then daily, the likelihood of needing surgery for people admitted to hospital with acute severe ulcerative colitis.</b></p> <p><b>20. Be aware that there may be an increased likelihood of needing surgery for people with any of the following:</b></p> <ul style="list-style-type: none"> <li>• stool frequency more than 8 per day</li> <li>• pyrexia</li> <li>• tachycardia</li> <li>• an abdominal X-ray showing colonic dilatation</li> <li>• low albumin, low haemoglobin, high platelet count or C-reactive protein (CRP) above 45 mg/litre (bear in mind that normal values may be different in pregnant women).</li> </ul>
Relative values of different outcomes	<p>The outcomes measured were discrimination (sensitivity and specificity) and calibration (observed/expected results) including area under the curve (AUC).</p> <p>The GDG considered high sensitivity on day 3, identifying those who need surgery, and high specificity on day 5, identifying those who do not need surgery, as the most important measures.</p>
Trade off between clinical benefits and harms	<p>There is a benefit in having a prognostic risk tool that will identify those people who are likely to need surgery when presenting with acute severe ulcerative colitis.</p> <p>The GDG recognised that there are harms associated with a high false positive rate (unnecessarily identifying someone as needing surgery). Secondary therapy would be</p>

	<p>initiated earlier and there would be higher surgical rates, resulting in higher costs, adverse events and lower quality of life.</p> <p>There are also harms associated with a high false negative rate (not identifying someone who needs surgery). Secondary therapy may be started too late. As a result, there may be a higher surgery rate potentially leading to higher financial costs, adverse events and lower quality of life. A greater risk of surgical complications as the patients may be sicker and a higher risk of mortality.</p> <p>The GDG noted that due to the low quality evidence and heterogeneity in the validation of the indices no one tool could be recommended for use over another to predict the likelihood of surgery. However, the GDG noted the tools all used similar variables (stool frequency, abdominal x-ray, CRP, haemoglobin, albumin) to predict the likelihood of surgery and felt these should be signposted as key clinical parameters to be measured on and during admission for people with acute severe ulcerative colitis. In addition, the GDG considered in their clinical experience there were other key clinical indicators that should also be monitored (temperature, heart rate, platelet count).</p>
Economic considerations	<p>The variables of the tools assessed in the review include stool frequency, abdominal x-ray, CRP, haemoglobin and albumin. The GDG noted that monitoring these parameters would be routine, especially for patients admitted under acute settings. The potential additional impact on resource use of recommending monitoring was considered to be minimal.</p>
Quality of evidence	<p>Seven studies were included in the review. These included 4 indexes that were developed to predict the colectomy rates associated with acute severe ulcerative colitis; Ho index, Travis index (Oxford Index), Seo index and the Lindgren index (Fulminant Colitis Index, FCI). The validation of the indexes is rated as low quality. There were considerable limitations:</p> <ul style="list-style-type: none"> <li>• Different populations: moderate to severe, severe, steroid refractory, use of infliximab</li> <li>• Different interventions were used (corticosteroids, aminosalicylates, infliximab, ciclosporin) or concomitant medications</li> <li>• Different time points used for colectomy (during admission, 30 days, 30 weeks, 3 months)</li> <li>• The cut off points and the point at which the data is recorded is different in the derivation and validation studies</li> <li>• None of the studies reported calibration data (observed and expected results)</li> <li>• Colonic dilatation measured in the Ho index is not easily defined in the children and young person population</li> <li>• In all of the studies, blinding was unclear</li> <li>• The Travis index needs to be considered separately as the index measure is binary (yes/no)</li> </ul> <p>The confidence intervals overlapped in the studies which reported the AUROC. One reason for this could be due to the different time and cut off points used, making the results difficult to interpret.</p>
Other considerations	<p>The GDG concluded that due to the considerable limitations, they could not confidently choose which index is superior in predicting the need for surgery in people with acute severe ulcerative colitis. The recommendations were based on the risk factors identified in the tools and GDG consensus based on clinical experience. It was noted in the limitations that the Ho index used colonic dilatation, which may be more difficult to judge in children and young people. The GDG noted the Paediatric Ulcerative Colitis Activity Index (PUCAI) is used in practice to assess the severity of disease on admission. This index was not included in the review because</p>

only one study was identified - this compared the PUCAI to other indexes; a derivation study was not identified.

**Research recommendations**

The GDG discussed making a research recommendation around validating the PUCAI for assessing the likelihood of surgery. The GDG also agreed that there is a need to develop and validate a risk tool for adults. For further information on the research recommendations see Appendix M.

## 6 Information on surgery

### 6.1 Clinical introduction

Ulcerative colitis affects different people in different ways and to differing extents. The effect is not limited to physical manifestations but can have emotional, psychological and social consequences.

Information-giving, including sign-posting, is one aspect of support that may help an individual address issues such as coming to terms with a new diagnosis, low mood, tiredness and coping skills, quality of life, effects on family and friends, relationships, education, work and social difficulties. Provision of information enables people with ulcerative colitis to take an active role in management of their disease and symptoms.

The NICE guidance "Patient Experience in adult NHS Services (NICE Clinical Guideline 138)" highlights the need to treat people as individuals and to tailor their care accordingly. Points emphasised include the person having timely and appropriate access to the relevant healthcare professionals at the point of need. Work by a patient support group indicates that most patients want to understand their condition and be involved in making decisions about long term treatment options.

Rapid access to specialist advice and care which is generally provided by IBD specialist nurses is advisable. This may include a telephone advice and support service, ensuring prompt and appropriate care. Specialist pharmacists are increasingly providing patient-centred care, particularly where immunosuppression and biological treatments are used.

While there is little evidence that diet plays a significant role in ulcerative colitis, many patients find it difficult to accept that this is the case. Dieticians can help patients understand the need for a balanced diet and can provide nutritional assessment, advice and support for people throughout the disease process.

Access to psychologists and counsellors is important for a range of problems and people with ulcerative colitis may benefit from their input at various stages of the disease. Improved access to these services has been recommended by the IBD Standards Group and the British Society of Gastroenterology. The effectiveness of their role, however, awaits rigorous evaluation.

The GDG also felt it important to address the issue of information that would be helpful in informing decisions about the timing of surgery. The need for surgery as an emergency is addressed in section 5.47. However, some people with frequent flares, chronic active disease or troublesome drug side effects may wish to consider surgery to improve their quality of life.

### 6.2 Review question: For adults, children and young people with ulcerative colitis considering surgery, what information on short and long term outcomes should be offered to patients and their carers by healthcare professionals?

For full details see review protocol in Appendix C.

### 6.3 Clinical evidence

No good quality studies were found directly addressing what people with ulcerative colitis wanted with regard to information and support when considering surgery. Consequently, we extracted data from more general qualitative studies on people's views and experience. One qualitative study and

one survey were included in the review.<sup>35,157</sup> See Table 80, the study selection flow chart in Appendix E, study evidence tables in Appendix G and exclusion list in Appendix F.

**Table 80: Study details and quality assessment**

Study	Population	Aims of the study	Methods	Analysis	Relevance to guideline population
CARLSSON2003 <sup>35</sup>	6/21 patients had ulcerative colitis.  Adequately reported	To describe the worries and concerns of IBD patients with an ileostomy  Adequately reported	Methods not appropriate to meet aims or for the population sample size.  Poorly reported It is unclear how the questionnaire was administered.	Poorly reported	Sweden. The population was post-operative. The time from surgery ranged from 2-39 years.  Indirect population
NOTTER2006 <sup>157</sup>	50 women after surgery  Poorly reported	To explore and describe the perceptions and experiences of women undergoing restorative proctocolectomy surgery  Well reported	Purposive sample Semi structured interview  Well reported and appropriate to aims	Phenomenological approach  Well reported	UK, Denmark. Only women It is unclear how many of the women had ulcerative colitis.  Limited sample and potentially Indirect sample

As there were limited studies identified, a call for evidence to stakeholders was carried out to try and identify any further studies that has not been retrieved in the searches or that were due for publication in the near future.

Five stakeholders responded to the call for evidence; The Royal College of Paediatrics and Child Health, Merck, Royal College of Nursing, British Society of Gastroenterology and Abbott Pharmaceuticals.

In total 52 pieces of evidence were submitted in the form of studies and surveys. Out of these only one survey fitted the inclusion criteria, the Inflammatory Bowel Disease Specialist Nurse Patient's Survey<sup>2</sup>. See Table 81 for a summary of the study.

Most of the submitted studies were excluded as they evaluated post-operative complications or changes in quality of life and not patient reported perspectives on information they would like to have known prior to surgery. The focus of this question was to identify the key issues that patients would like to know about before making the decision to have surgery.



**Table 81: Summary of the submitted study's details and quality assessment**

Study	Population	Aims of the study	Methods	Analysis	Relevance to guideline population
ANDERSON2008 <sup>2</sup>	Patients with inflammatory bowel disease in the United Bristol Healthcare NHS Trust using the new dedicated IBD surgical clinic.  Poorly reported	To find out how patients felt about the new dedicated IBD surgical clinic  Well reported	Questionnaire sent with a pre-paid return envelope.  It is unclear whether this has been previously validated	Percentage agreement for each question Free text/ comments	U.K.  Indirect population as it is an IBD population

### Themes identified

Table 82 lists the themes identified in the studies.

**Table 82: Identified themes in the studies**

Study	Themes identified
ANDERSON2008 <sup>2</sup>	<ul style="list-style-type: none"> <li>Information on the surgery available for reference post consultation</li> <li>Benefits of having access to an IBD nurse</li> <li>Help with diet and emotional support</li> </ul>
CARLSSON2003 <sup>35</sup>	<ul style="list-style-type: none"> <li>Intimacy (Ranked 1<sup>st</sup>)</li> <li>Access to quality medical care(Ranked 2<sup>nd</sup>)</li> <li>Energy level(Ranked 3<sup>rd</sup>)</li> <li>Loss of sexual drive (Ranked 4<sup>th</sup>)</li> <li>Producing unpleasant odours (Ranked 5.5<sup>th</sup>)</li> <li>Being a burden on others (Ranked 5.5<sup>th</sup>)</li> <li>Ability to perform sexually (Ranked 7<sup>th</sup>)</li> <li>Attractiveness (Ranked 8.5<sup>th</sup>)</li> <li>Feelings about my body (Ranked 8.5<sup>th</sup>)</li> <li>Uncertain nature of disease (Ranked 10<sup>th</sup>)</li> </ul>
NOTTER2006 <sup>157</sup>	<ul style="list-style-type: none"> <li>Counselling or psychological support for the patients, their partners and families</li> <li>Majority of patients were not told (or did not remember) everything to expect. The patients recall of information and its retention should be checked</li> <li>Patients had a memory of the pain endured, body changes and the actual loop ileostomy itself. It was not what they had anticipated</li> <li>Few knew what a loop or temporary ileostomy would look like and were quite shocked</li> <li>Specialist nursing support was good, sometimes the ward staff were unclear what to do and patient's treatment/ addressing of their problems would have a time delay until a stoma nurse was available</li> <li>Importance of adequate analgesia</li> </ul>

## 6.4 Summary of the evidence

The evidence highlights the need for people considering surgery to have access to healthcare professionals who have expertise in ulcerative colitis surgery. There was specific reference to the specialist nursing team. This enables the patient to discuss any anxieties that they may have about the procedures. Additional literature for patients to refer to also appeared to be an important factor. Sufficient preparation needs to be made for people to fully understand the surgical procedures and the changes that may occur in terms of body image and effect on daily activities. It is important to involve family members, parents or carers as appropriate and ensure that they also have access to sufficient information and support.

## 6.5 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

**Table 83: Resource costs**

Healthcare professional	Costs per hour of patient contact <sup>(a)</sup>
Medical/surgical consultant	£137
General practitioner	£127
IBD nurse specialist	£53
Specialist registrar	£59

(a) PSSRU 2011<sup>45</sup>

## 6.6 Recommendations and link to evidence

<b>Recommendations</b>	<p><b>Information about treatment options for people who are considering surgery</b></p> <p>These recommendations apply to anyone with ulcerative colitis considering elective surgery. The principles can also be applied to people requiring emergency surgery.</p> <p><b>Information when considering surgery</b></p> <p><b>21. For people with ulcerative colitis who are considering surgery, ensure that a specialist (such as a gastroenterologist or a nurse specialist) gives the person (and their family members or carers as appropriate) information about all available treatment options, and discusses this with them. Information should include the benefits and risks of the</b></p>
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	<p>different treatments and the potential consequences of no treatment.</p> <p><b>22.Ensure that the person (and their family members or carers as appropriate) has sufficient time and opportunities to think about the options and the implications of the different treatments.</b></p> <p><b>23.Ensure that a colorectal surgeon gives any person who is considering surgery (and their family members or carers as appropriate) specific information about what they can expect in the short and long term after surgery, and discusses this with them.</b></p> <p><b>24.Ensure that a specialist (such as a colorectal surgeon, a gastroenterologist, an inflammatory bowel disease nurse specialist or a stoma nurse) gives any person who is considering surgery (and their family members or carers as appropriate) information about:</b></p> <ul style="list-style-type: none"> <li>• diet</li> <li>• sensitive topics such as sexual function</li> <li>• effects on lifestyle</li> <li>• psychological wellbeing</li> <li>• the type of surgery, the possibility of needing a stoma and stoma care.</li> </ul> <p><b>25.Ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives any person who is having surgery (and their family members or carers as appropriate) specific information about the siting, care and management of stomas.</b></p> <p><b>Information after surgery</b></p> <p><b>26.After surgery, ensure that a specialist who is knowledgeable about stomas (such as a stoma nurse or a colorectal surgeon) gives the person (and their family members or carers as appropriate) information about managing the effects on bowel function. This should be specific to the type of surgery performed (ileostomy or ileoanal pouch) and could include the following:</b></p> <ul style="list-style-type: none"> <li>• strategies to deal with the impact on their physical, psychological and social wellbeing</li> <li>• where to go for help if symptoms occur</li> <li>• sources of support and advice.</li> </ul>
Relative values of different outcomes	<p>The outcomes of interest for this review were those reported in the papers that were relevant to identifying information that people want when considering elective surgery.</p> <p>The outcomes were categorised into short term or long term outcomes, subcategorised by biological, physical/ interference with daily activities or psychological concerns.</p> <p>The GDG considered any reported opinions of information-provision equally important. The recommendation was based on this information and consensus opinion.</p>
Trade off between	The GDG considered that people are often poorly prepared for surgery. The benefit

clinical benefits and harms	<p>of receiving good quality information, tailored to a person's needs and given by a professional who is knowledgeable in the condition is well recognised.</p> <p>In this situation no harms were identified in giving appropriate information.</p> <p>Healthcare professionals must be aware of the impact of information on patients. This may have a negative impact or may be misunderstood and healthcare professionals should check the understanding and recall of information that has been given.</p>
Economic considerations	<p>The GDG discussed patient information in the context of routine healthcare practice. It was expected that any impact on time and resource use would be minimal and would likely be offset by an improvement in quality of life.</p>
Quality of evidence	<p>Two low quality studies were identified and the call for evidence identified one additional survey. The studies identified were of limited use in supporting the GDG in making a recommendation, Carlsson 2003 included only six people with ulcerative colitis whilst Notter 2006 only included women and it was unclear how many of these women had ulcerative colitis. The IBD nurse survey had a mixed IBD population and was of a small sample size.</p>
Other considerations	<p>The GDG considered this evidence and, in their experience, thought that many important areas people would like information on had not been identified. The additional areas identified by the GDG are listed below and are the basis for the consensus recommendation. The GDG were keen to highlight that it is important to give people realistic information about what to expect after surgery and not just the benefits of surgery. This will enable them to successfully manage their expectations of quality of life after surgery.</p> <p><b><u>Information on short term outcomes</u></b></p> <p><b>Biological - Information on:</b></p> <ul style="list-style-type: none"> <li>• Proposed surgery including any medical alternatives</li> <li>• Type of surgery and technique</li> <li>• The possibility of needing a stoma</li> <li>• Short term risks and complications</li> <li>• Time in hospital</li> </ul> <p><b>Physical – Information on:</b></p> <ul style="list-style-type: none"> <li>• Likely recovery time and ability to return to work</li> </ul> <p><b>Psychological needs – Information on:</b></p> <ul style="list-style-type: none"> <li>• Initial reaction to a stoma and perception of their body</li> <li>• The impact on immediate quality of life</li> </ul> <p><b><u>Information on long term outcomes</u></b></p> <p><b>Biological - Information on:</b></p> <ul style="list-style-type: none"> <li>• Complications (hernia, blockage, leakage, pouchitis, poor function)</li> <li>• Diagnosis (risk of diagnosis actually being Crohn's disease, therefore risk of recurrence)</li> <li>• Potential need for additional surgery (rectal stump removal, stoma reversal etc.)</li> <li>• Management of the stoma or pouch</li> <li>• Sexual function (impaired erection, ejaculation problems, discomfort for women after total proctocolectomy from loss of support of the posterior vagina)</li> <li>• Risk of nerve damage (bladder and sexual dysfunction)</li> <li>• Fertility and pregnancy (mode of delivery)</li> </ul> <p><b>Physical impact – Information on:</b></p> <ul style="list-style-type: none"> <li>• Restrictions on "normal" activities, work etc. for example swimming</li> <li>• Impact on diet</li> <li>• Ability to self-care</li> </ul>

- Skin care
- Stoma counselling (impact of appliances and stool frequency)

**Psychological needs – Information on:**

- Emotional aspects of living with a stoma (getting used to it)
- Impact on quality of life (social, occupational, sexual, functioning, relationships)
- Self-image and others perception of you
- Scar/ stoma
- Awareness of cultural differences

In the GDG's experience these were key areas that people value in their consultations. This list is not exhaustive, but as a minimum these areas should be included in the discussion with the person considering surgery. The GDG recognised that some healthcare professionals may avoid discussing certain issues; they may not have the expertise in that area or assume that others will discuss it. The GDG are keen to emphasize that healthcare professionals should be adequately supported to address these issues. The GDG noted that people often request to speak to someone who has had the surgery and seek advice on support groups.

The GDG discussed who is best placed to give information to people considering surgery. The GDG agreed that in the case of preparing people for major bowel surgery, where the impact is significant and timing is important, it is crucial that this is given by someone who has detailed specialist knowledge and experience in this area and is therefore able to address any questions that someone considering surgery may ask. The GDG have given examples of healthcare professionals that have advanced skills and knowledge specific to this area.

**Research recommendation**

The GDG agreed that the lack of evidence on information about surgery that people with ulcerative colitis would wish to know justified developing a research recommendation. For further information on the research recommendations see Appendix M.

## 7 Maintaining remission in people with ulcerative colitis

### 7.1 Clinical introduction

Ulcerative colitis is a long-term inflammatory illness affecting the colonic mucosa, which most commonly runs a relapsing and remitting course. This means that periods where the symptoms and inflammation in the colon and/or rectum are settled remission and these periods are interspersed with episodes when the symptoms and inflammation are more active - relapses. Guidance on treatment of relapses, or the induction of remission, is covered in Chapter 5.

Two main groups of drugs are used to try to maintain remission: aminosalicylates and immunomodulators.

5-aminosalicylic acid (5-ASA) is generally regarded as the active moiety of aminosalicylate preparations used in ulcerative colitis. There are many preparations/or brands of 5-ASA that are designed to release the active drug, 5-ASA, in different parts of the small intestine or colon. The clinical significance of this remains unclear. In addition, there remains uncertainty as to the importance of the dose of aminosalicylate used for maintenance of remission in ulcerative colitis. Aminosalicylate and corticosteroid preparations can also be administered topically - as enemas or suppositories. Although thought to be infrequent, significant or severe side-effects of aminosalicylates include pancreatitis and kidney disease.

Immunomodulator medication (azathioprine, mercaptopurine, methotrexate and tacrolimus) may also play a role in maintenance of remission. In this context, these drugs have been used for disease that is difficult to control: where the condition relapses rapidly after successful induction of remission; when symptoms relapse on decreasing treatment with steroids, or after a severe flare. These drugs may be associated with significant side-effects and monitoring for these is required.

In any long-term condition, potentially requiring medication to be taken for a prolonged period, attempts to promote adherence to medication are important. These might include the dosing regimen, good quality information and explanation about the medication.

It is therefore important to consider whether these drugs are effective in maintaining remission, and their relative safety, toxicity and cost-effectiveness.

In evaluating the evidence on maintenance of remission, the GDG had to consider how relapse was defined. A large number of definitions are used in clinical trials,<sup>215</sup> using clinical features, with or without endoscopic features, and attempts continue to move towards a more uniform definition.<sup>215</sup> In order to ensure that important studies were not excluded from their review, the GDG agreed, a priori, to use the authors' definition of relapse, rather than to attempt to utilise a single index or definition. This does however risk increasing the heterogeneity of the studies included.

### 7.2 Review question: In adults, children and young people with ulcerative colitis in remission, what is the clinical and cost-effectiveness of corticosteroids, aminosalicylates, immunomodulators (mercaptopurine, azathioprine, methotrexate and tacrolimus) for the maintenance of remission compared to

**themselves (different preparations and doses), each other, combinations of preparations (oral and topical) and placebo?**

For full details see review protocol in Appendix C.

A matrix showing where evidence was identified is given in Table 84. A cross in the box indicates evidence was found and the evidence has been reviewed in this chapter an empty box indicates no evidence was found.





The reviews for the maintenance of remission are presented in the following order:

- Topical aminosalicylates versus placebo, topical aminosalicylates versus topical aminosalicylates dose comparison (section 7.4.1)
- Topical corticosteroids versus placebo (section 7.8.1)
- Oral aminosalicylates versus placebo, oral aminosalicylates versus oral aminosalicylates comparisons; dose, preparations, regimen and regimen and dose (section 7.12.1)
- Continuous oral aminosalicylates versus intermittent topical aminosalicylates (section 7.16.1)
- Immunomodulators: azathioprine versus placebo, azathioprine versus aminosalicylates, methotrexate versus placebo, mercaptopurine versus placebo and mercaptopurine versus 5-ASA (section 7.22.1).

No studies were identified for the use of oral corticosteroids in maintenance treatment that met the inclusion criteria for the review.

For all the reviews in this chapter an author defined definition of relapse was used. There is an extensive number of different indices used in the published literature and many of these indices are not validated. This approach carries a high risk of bias however, by choosing one index the GDG felt that too many studies would be excluded and there would be a lack of evidence to consider. The bias associated with using the author's definitions was taken into account when analysing the data. There were no setting restrictions. Minimum trial duration of 6 months was applied.

The following strata were analysed for each outcome if the data were available:

- Severity of previous relapse (mild to moderate or severe)
- Frequency of relapses
- Current use of immunomodulators prior to the trial.

The following subgroups were considered for subgroup analysis when appropriate in the event of heterogeneity in the meta-analysis:

- Age (adults, children and young people)
- Mechanism of release (for oral ASAs).

### 7.3 Clinical evidence: Topical aminosalicylates

Three studies were included in the review<sup>47,49,138</sup>. Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

## 7.4 Evidence profile

### 7.4.1 Topical aminosalicylates versus placebo (continuous)

Table 85: Topical aminosalicylates versus placebo (continuous)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical ASAs (continuous treatment)	Placebo (continuous treatment)	Relative (95% CI)	Absolute		
Relapse - 500mg mesalazine vs. placebo												
1	randomised trials	serious <sup>1,2,3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	11/40 (27.5%)	14/35 (40%)	HR 0.53 (0.24 to 1.17)	163 fewer per 1000 (from 285 fewer to 50 more)	⊕⊕⊕⊕ LOW	CRITICAL
Relapse - 800mg mesalazine vs. placebo												
1	randomised trials	very serious <sup>2,5</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/15 (6.7%)	11/15 (73.3%)	HR 0.03 (0 to 0.25)	694 fewer per 1000 (from 452 fewer to 733 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Relapse - 1g mesalazine vs. placebo												
1	randomised trials	serious <sup>1,2,3</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/36 (8.3%)	14/35 (40%)	HR 0.18 (0.05 to 0.63)	312 fewer per 1000 (from 125 fewer to 375 fewer)	⊕⊕⊕⊕ MODERATE	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events - 500mg mesalazine versus placebo												
1	randomised trials	serious <sup>1,2,3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4,6</sup>	none	2/35 (5.7%)	1/29 (3.4%)	RR 1.66 (0.16 to 17.37)	23 more per 1000 (from 29 fewer to 564 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 1g mesalazine versus placebo												
1	randomised trials	serious <sup>1,2,3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4,6</sup>	none	2/32 (6.3%)	1/29 (3.4%)	RR 1.81 (0.17 to 18.95)	28 more per 1000 (from 29 fewer to 619 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Unclear method of randomisation.

<sup>2</sup> Unclear allocation concealment.

<sup>3</sup> Stated to be double blind, but no details were given.

<sup>4</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>5</sup> Open study.

<sup>6</sup> Crosses the upper (1.25) relative risk (RR) MID.

**Table 86: Topical aminosalicylates versus placebo (intermittent)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical ASAs (intermittent treatment)	Placebo (intermittent treatment)	Relative (95% CI)	Absolute		
Relapse at 1 year												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/48 (20.8%)	24/47 (51.1%)	RR 0.41 (0.22 to 0.76)	301 fewer per 1000 (from 123 fewer to 398 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	6/48 (12.5%)	5/47 (10.6%)	RR 1.17 (0.38 to 3.59)	18 more per 1000 (from 66 fewer to 276 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Stated to be double blind but no further details were given. High drop out rate. Mean duration of previous relapse was unbalanced between the two groups.

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>3</sup> Crosses the upper (1.25) relative risk (RR) MID.

**Table 87: Topical aminosalicylates versus topical aminosalicylates (dose comparison)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical ASA (lower dose)	Topical ASA (higher dose)	Relative (95% CI)	Absolute		
Relapse - 500mg mesalazine vs. 1g mesalazine												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	11/40 (27.5%)	3/36 (8.3%)	HR 4.00 (1.12 to 14.33)	211 more per 1000 (from 10 more to 629 more)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events												

1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	2/35 (5.7%)	2/32 (6.3%)	RR 0.91 (0.14 to 6.12)	6 fewer per 1000 (from 54 fewer to 320 more)	⊕○○○ VERY LOW	IMPORTANT
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<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Stated to be double blind but no further details were given.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>3</sup> Crosses the lower (0.75) and the upper (1.25) relative risk (RR) MIDs.

## 7.5 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 7.6 Evidence statements

### 7.6.1 Clinical evidence statements

#### 7.6.1.1 Topical aminosalicylates versus placebo (continuous)

##### Relapse

Topical ASAs (500mg) may be clinically more effective in reducing relapse rates compared to placebo, 800mg and 1g are clinically more effective in reducing relapse rates compared to placebo [Moderate to low quality evidence, 1 study, N=75; 1 study, N=30, 1 study, N=71]

##### Adverse events

There may be no clinical difference between topical ASAs (500mg, 1g) and placebo in adverse event rates [very low quality evidence, 1 study, N=64, 1 study, N=61]

#### 7.6.1.2 Topical aminosalicylates versus placebo (intermittent)

##### Relapse

Intermittent topical ASAs may be clinically more effective in reducing relapse rates compared to placebo at 1 year [low quality evidence, 1 study, N=95]

##### Adverse events

There may be no clinical difference in adverse event rates between intermittent topical ASAs and placebo at 1 year [very low quality evidence, 1 study, N=95]

#### 7.6.1.3 Topical aminosalicylates versus topical aminosalicylates (dose comparison)

##### Relapse

1g topical ASAs may be clinically more effective in reducing relapse rates compared to 500mg topical ASA [low quality evidence, 1 study, N=76]

##### Adverse events

There may be no clinical difference in adverse event rates between 500mg and 1g of topical ASAs [very low quality evidence 1 study, N=67]

### **7.6.2 Economic evidence statements**

No relevant economic evaluations were identified.

## **7.7 Clinical evidence: Topical corticosteroids**

One study was included in the review.<sup>127</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

## 7.8 Evidence profile

### 7.8.1 Topical corticosteroids versus placebo

**Table 88: Topical corticosteroids versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical steroid (budesonide) twice a week	Placebo twice a week	Relative (95% CI)	Absolute		
Relapse rate at 24 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	16/39 (41%)	19/37 (51.4%)	RR 0.8 (0.49 to 1.3)	103 fewer per 1000 (from 262 fewer to 154 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	28/39 (71.8%)	24/37 (64.9%)	RR 1.11 (0.81 to 1.51)	71 more per 1000 (from 123 fewer to 331 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Unclear method of randomisation, allocation concealment and blinding. No baseline characteristics given.

<sup>2</sup> Crosses the lower (0.75) and upper (1.25) relative risk (RR) MIDs.

<sup>3</sup> Crosses the upper (1.25) relative risk (RR) MID.

## 7.9 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## 7.10 Evidence statements

### 7.10.1 Clinical evidence statements

#### 7.10.1.1 Relapse at 24 weeks

Topical steroids (budesonide twice a week) may be clinically more effective at reducing relapse rates at 24 weeks compared to placebo [very low quality evidence 1 study, N=76]

#### 7.10.1.2 Adverse events

There was no clinical difference in adverse event rates between topical steroids (budesonide twice a week) and placebo [very low quality evidence 1 study, N=76]

### 7.10.2 Economic evidence statements

No relevant economic evaluations were identified.

## 7.11 Clinical evidence: Oral aminosalicylates

Thirty five studies were included in the review.<sup>7,9,12,44,52,58,59,74,75,83,90,92,93,99,101,106,108-111,113,114,116,144,145,154,163,169,175,177,178,187,188,213,229</sup>

Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

The BNF states that: The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable. In order to address this, mesalazines were compared to each other where possible and disease extent was explored where heterogeneity was present. The oral mesalazines listed in the BNF are Asacol, Ipocol, Mesren, Mezavant XL, Octasa, Pentasa and Salofalk. The reviews in this guideline name the mesalazine as it is named in the studies. We are aware that the mesalazines can change brand names, for example Mesren was been rebranded as Octasa 400 in December 2012.

The mesalazines were also compared to the ASAs where possible. The mesalazines named in the included studies were Asacol, Mezavant XL, Pentasa and Salofalk. The other ASAs in the included studies were balsalazide, olsalazine and sulphasalazine.



“Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis” was published by the Cochrane collaboration in 1997 and has since been updated several times most recently in 2012.<sup>65</sup> The review included 38 studies, which looked at the following comparisons:

- 5-ASAs versus placebo
- 5-ASAs versus sulphasalazine
- Once a day versus conventional dosing
- 5-ASA versus comparator 5-ASA
- 5-ASA dose ranging

The Cochrane review concluded that 5-ASA was clinically more effective than placebo for the maintenance therapy of ulcerative colitis, sulphasalazine was superior to 5-ASAs and once daily dosing is as effective as conventional dosing. No differences were found between the different formulations. It was also suggested that patients with extensive disease or frequent relapses may benefit from a higher dose of oral ASA. The adverse events rates did not appear to differ between the higher and the lower dose. The Cochrane review was excluded because it differed from the clinical review protocol in terms of the methods of analysis; the clinical review used hazard ratios in preference to relative risk ratios to take account of the time horizon, included trials with doses under the level recommended in the BNF which was considered inconsistent with clinical practice and treatments that are not available in the UK. The following studies included in the Cochrane review were excluded from the Ulcerative Colitis review for the following reasons:

- ANDREOLI1987, FOCKENS1995, GIAFFER1992, MCINTYRE1988; MULDER1988: dose is lower than that recommended in the BNF
- ARDIZZONE1995, LICHTENSTEIN2010, MAHMUD2002; RUTGEERTS1989: comparator is not available in the UK (Claversal, Apriso granules, Asacolon)
- DEW1983: Unclear method of randomisation.

## 7.12 Evidence profile

### 7.12.1 Oral aminosalicylates versus placebo

Table 89: Oral aminosalicylates versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral ASAs	Placebo	Relative (95% CI)	Absolute		
Relapse												
4	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/264 (31.4%)	143/272 (52.6%)	HR 0.53 (0.41 to 0.7)	199 fewer per 1000 (from 119 fewer to 262 fewer)	⊕⊕○○ LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events												
3	randomised trials	very serious <sup>2</sup>	serious <sup>3</sup>	no serious indirectness	serious <sup>4</sup>	none	51/169 (30.2%)	36/170 (21.2%)	RR 1.42 (1.00 to 2.01)	89 more per 1000 (from 0 more to 214 more)	⊕○○○ VERY LOW	IMPORTANT
Serious adverse events												
1	randomised trials	very serious <sup>5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4,6</sup>	none	1/87 (1.1%)	1/87 (1.1%)	OR <sup>7</sup> 1.00 (0.06 to 16.12)	0 fewer per 1000 (from 11 fewer to 146 more) <sup>8</sup>	⊕○○○ VERY LOW	IMPORTANT
Hospitalizations												
1	randomised trials	very serious <sup>9</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	6/99 (6.1%)	1/111 (0.9%)	RR 6.73 (0.82 to 54.91)	52 more per 1000 (from 2 fewer to 486 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Some studies were stated to be double blind, no further details were given in the papers. >10% difference in missing data between some treatment arms.

<sup>2</sup> Overall unclear method of randomisation and allocation concealment. No baseline characteristics and unclear drop out rate in one study.

<sup>3</sup>  $I^2 > 50\%$  but  $< 75\%$ .

<sup>4</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>5</sup> Unclear allocation concealment. Stated to be double blind, but no further details were given. Unclear drop out rate.

<sup>6</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>7</sup> Peto odds ratio

<sup>8</sup> Risk difference

<sup>9</sup> Unclear method of randomisation. The study has an unequal number of patients with distal disease in each treatment arm, double blind, but no further details were given.

### Subgroup analysis

Heterogeneity was present for adverse events (74%) between the three studies; DISSANAYAKE1973<sup>59</sup>, HANAUER1996A<sup>83</sup> and WRIGHT1993<sup>229</sup>. They all used different aminosalicylates which were sulphasalazine, mesalazine (Asacol) and olsalazine respectively, which may account for the differences. In terms of age group, both the HANAUER1996A<sup>83</sup> and WRIGHT1993<sup>229</sup> studies were 18-75years and the DISSANAYAKE1973<sup>59</sup> did not provide any baseline characteristics or inclusion/exclusion criteria on age group.

### Additional information which could not be meta-analysed:

#### Relapse

A hazard ratio was unable to be calculated for the DISSANAYAKE1973<sup>59</sup> study. At 6 months the relative risk ratio supports the use of an oral ASA (sulphasalazine was used in the study) compared to placebo (RR: 0.22 (0.08, 0.58)) in this withdrawal trial.

In the HAWKEY1997<sup>90</sup> study, a Kaplan Meier curve demonstrating the proportion of patients remaining in remission for the two treatment groups over 6 months do not overlap,  $p < 0.001$  for all evaluable patients.

The median time to relapse was reported in the RIIS1973<sup>175</sup> study, which were 93 days in the sulphasalazine group and 102 in the placebo group. At 6 months the relative risk ratio for relapse was 0.82 (0.32, 2.10) demonstrating no clinical difference between the sulphasalazine and placebo arms.

The SANDBERGERTZEN1986<sup>187</sup> found oral ASAs (olsalazine) to have a lower relapse rate compared to placebo, relative risk ratio 0.51 (0.29, 0.92). In the WRIGHT1993<sup>229</sup> study the median time to relapse was 342 days in the olsalazine group and 100 days in the placebo group.

#### Adverse events

ARDIZZONE1999C<sup>7</sup> study only reported withdrawals due to adverse events. There were 3 in the mesalazine group (due to abdominal pain, bloating and diarrhoea) and 2 in the placebo group (abdominal pain and bloating).

MINER1995<sup>144</sup> only reported treatment related adverse events. There were 34 withdrawals due to adverse events in the mesalazine group and 14 in the placebo group. Doesn't state what they were for each group, just the most frequent reasons, which were: abdominal pain (n=1), nausea (n=1), hepatitis (n=1, thought to be drug-related) in the mesalazine group and headache (2 patients) in the placebo group.

MISIEWICZ1965<sup>145</sup> study only reports withdrawals due to adverse events. These were: sulphasalazine group (3 due to nausea and abdominal pain), placebo group (1 due abdominal pain).

**Table 90: Oral ASAs versus oral ASAs (dose comparison) - Asacol**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose of Asacol	Higher dose of Asacol	Relative (95% CI)	Absolute		
Relapse (dichotomous) - 1.2g versus 2.4g at 12 months												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	48/76 (63.2%)	48/80 (60%)	RR 1.05 (0.82 to 1.35)	30 more per 1000 (from 108 fewer to 210 more)	⊕○○○ VERY LOW	CRITICAL
Relapse at 1 year (dichotomous) by relapse frequency - 1.2g versus 2.4g (≤3 relapses/ year)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	16/36 (44.4%)	0/16 (0%)	RR 15.16 (0.97 to 238.19)	-	⊕○○○ VERY LOW	CRITICAL
Relapse at 1 year (dichotomous) by relapse frequency - 1.2g versus 2.4g (>3 relapses/year)												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	32/40 (80%)	48/64 (75%)	RR 1.07 (0.86 to 1.32)	53 more per 1000 (from 105 fewer to 240 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events - 1.2g versus 2.4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	0/76 (0%)	1/80 (1.3%)	OR <sup>4</sup> 0.14 (0.00 to 7.18)	<sup>5</sup> 10 fewer per 1000 (from 50 fewer to 20 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Single blind.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>3</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>4</sup> Peto odds ratio

<sup>5</sup> Absolute risk difference was calculated

**Table 91: Oral ASAs versus oral ASAs (dose comparison) - Salofalk**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose of Salofalk	Higher dose of Salofalk	Relative (95% CI)	Absolute		
Relapse by 1 year (dichotomous) - 1.5g versus 3.0g												
1	randomised trials	no serious risk of bias <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/212 (20.8%)	17/217 (7.8%)	RR 2.65 (1.56 to 4.49)	129 more per 1000 (from 44 more to 273 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life												

0	No evidence available					none	-	-	-	-		CRITICAL
<b>Adverse events - 1.5g versus 3.0g</b>												
1	randomised trials	no serious risk of bias <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	117/212 (55.2%)	89/217 (41%)	RR 1.35 (1.1 to 1.64)	144 more per 1000 (from 41 more to 262 more)	⊕⊕⊕O MODERATE	IMPORTANT
<b>Serious adverse events - 1.5g versus 3.0g</b>												
1	randomised trials	no serious risk of bias <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	7/212 (3.3%)	8/217 (3.7%)	RR 0.9 (0.33 to 2.43)	4 fewer per 1000 (from 25 fewer to 53 more)	⊕⊕OO LOW	IMPORTANT

<sup>1</sup> Double blind, but no further information was given.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>3</sup> Crosses the lower (0.75) relative risk (RR) MID.

**Table 92: Oral ASAs versus oral ASAs (dose comparison) - Olsalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose of Olsalazine	Higher dose of Olsalazine	Relative (95% CI)	Absolute		
Relapse by 6 months (dichotomous) - 1.25g versus 2.0g												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	13/35 (37.1%)	5/34 (14.7%)	RR 2.53 (1.01 to 6.32)	225 more per 1000 (from 1 more to 782 more)	⊕⊕OO LOW	CRITICAL
Relapse by 12 months (dichotomous) - 1.0g versus 2.0g												
1	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	17/65 (26.2%)	10/62 (16.1%)	RR 1.62 (0.81 to 3.26)	100 more per 1000 (from 31 fewer to 365 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events - 1.25g olsalazine vs. 2.0g olsalazine												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,4</sup>	none	3/35 (8.6%)	6/34 (17.6%)	RR 0.49 (0.13 to 1.79)	90 fewer per 1000 (from 154 fewer to 139 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events - 1.0g olsalazine vs. 2.0g olsalazine												
1	randomised trials	very serious <sup>3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	26/65 (40%)	34/62 (54.8%)	RR 0.73 (0.5 to 1.06)	148 fewer per 1000 (from 274 fewer to 33 more)	⊕OOO VERY LOW	IMPORTANT

<sup>1</sup> Unclear allocation concealment. Stated to be double blind, no further details were given.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>3</sup> Overall unclear method of randomisation and allocation concealment. Unclear blinding. Unclear drop out rate.

<sup>4</sup> Crosses the lower (0.75) relative risk (RR) MID.

#### Additional information which could not be meta-analysed:

##### Relapse

In the TRAVIS1994<sup>213</sup> paper the median time to relapse was also reported which was 168 days (range 25-378), 174 days (range 14-365) and 191 days (range 50-287) for 0.5g, 1.0g and 2.0g of olsalazine respectively.

**Table 93: Oral ASAs versus oral ASAs (dose comparison) – Sulphasalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose of Sulphasalazine	Higher dose of Sulphasalazine	Relative (95% CI)	Absolute		
Relapse by 6 months (Dichotomous) - 2g versus 4g												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	8/57 (14%)	5/56 (8.9%)	RR 1.57 (0.55 to 4.51)	51 more per 1000 (from 40 fewer to 313 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Very limited baseline characteristics. Unclear blinding.

<sup>2</sup> Crosses the upper (1.25) MID.

<sup>3</sup> Crosses the lower (0.75) MID.

#### Additional information which could not be meta-analysed:

##### Adverse events

In the AZADKHAN1980<sup>9</sup> study the majority of the population were 2g SASP tolerant population. Only the adverse events for the 4g SASP were reported, which occurred in 21 out of 56 patients. Most of the side effects were said to have occurred during the first few weeks when the dose was being increased. Adverse events included; nausea (n=11), malaise (n=5), headache (n=4), myalgia (n=2), diarrhoea (n=2), constipation (n=1), anal soreness (n=2), anal mucous discharge (n=1), flatulence (n=2), dysuria (n=3), anorexia (n=2), indigestion (n=1), insomnia (n=1), dizziness (n=2).

**Table 94: Oral ASAs versus oral ASAs (dose comparison) – Balsalazide**

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Lower dose of	Higher dose of	Relative	Absolute		

studies		bias				considerations	Balsalazide	Balsalazide	(95% CI)			
<b>Relapse by 26 weeks -3g versus 6g</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	13/48 (27.1%)	3/40 (7.5%)	RR 3.61 (1.11 to 11.79)	196 more per 1000 (from 8 more to 809 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Relapse by 12 months - 3g versus 6g</b>												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,4</sup>	none	10/54 (18.5%)	15/54 (27.8%)	RR 0.67 (0.33 to 1.35)	92 fewer per 1000 (from 186 fewer to 97 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Adverse events - 3.0g balsalazide vs. 6.0g balsalazide</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	18/48 (37.5%)	21/40 (52.5%)	RR 0.71 (0.45 to 1.14)	152 fewer per 1000 (from 289 fewer to 73 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>3</sup> Overall unclear method of randomisation and allocation concealment. Double blind, but no further details were given.

<sup>4</sup> Crosses the lower (0.75) relative risk (RR) MID.

#### Additional information which could not be meta-analysed:

##### Relapse

In the GREEN1992<sup>74</sup> study, a hazard ratio was unable to be calculated, however the Kaplan Meier curve demonstrated the curves to cross each other, and were described as being not significant.

##### Adverse events

In the GREEN1992<sup>74</sup> study, only withdrawals due to adverse events were reported; 3g of balsalazide there were 6 withdrawals due to headache, nausea (2 patients), diarrhoea (2 patients) and abdominal pain, and in the 6g of balsalazide there were 3 due to nausea, diarrhoea and abdominal pain (2 patients). They all withdrew within the first seven weeks of the trial.

**Table 95: Oral ASAs versus oral ASAs (interclass comparison) – Olsalazine versus mesalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olsalazine	Mesalazine	Relative (95% CI)	Absolute		

Relapse - 1g olsalazine versus 1.2g mesalazine												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	5/49 (10.2%)	13/50 (26%)	HR 0.3 (0.11 to 0.84)	174 fewer per 1000 (from 37 fewer to 227 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Single blind.

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

### Additional information which could not be meta-analysed:

#### Adverse events

In the COURTNEY1992<sup>44</sup> study it was unclear whether the figures reported were the total number of adverse events, rather than the number of patients experiencing one or more adverse events. There were 6 in the olsalazine group and 5 in the mesalazine group; 9 probably/ definitely drug related adverse events (diarrhoea in 2 olsalazine patients (1 withdrew), 2 patients in each group had abdominal pain (both in the mesalazine group withdrew and were found to have duodenal ulcers and 1 from the olsalazine group withdrew), nausea and rash in 1 olsalazine patient and 2 mesalazine patients. At the end of the 12 months two patients had colon cancer, symptomless and small; one in each group. They had had ulcerative colitis for 14.5 and 19 years.

**Table 96: Oral ASAs versus oral ASAs (interclass comparison) – Olsalazine versus sulphasalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olsalazine	Sulphasalazine	Relative (95% CI)	Absolute		
Relapse - 1g olsalazine versus 2g sulphasalazine												
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	75/243 (30.9%)	65/243 (26.7%)	HR 1.36 (0.98 to 1.9)	78 more per 1000 (from 5 fewer to 179 more)	⊕⊕⊕⊕ LOW	CRITICAL
Relapse (dichotomous) - 1g olsalazine versus 2g SASP at 12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	46/98 (46.9%)	42/99 (42.4%)	RR 1.11 (0.81 to 1.51)	47 more per 1000 (from 81 fewer to 216 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Relapse (dichotomous) - 1.25g olsalazine versus 2g SASP at 6 months												
1	randomised trials	very serious <sup>3,4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	13/35 (37.1%)	11/40 (27.5%)	RR 1.35 (0.70 to 2.62)	96 more per 1000 (from 83 fewer to 445 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Relapse (dichotomous) - 2g olsalazine versus 2g SASP at 6 months												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	5/34 (14.7%)	11/40 (27.5%)	RR 0.53 (0.21 to 1.39)	129 fewer per 1000 (from 217 fewer to 107 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL



Relapse (dichotomous) - 2g olsalazine versus 4g SASP at 48 weeks												
1	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	6/23 (26.1%)	7/23 (30.4%)	RR 0.86 (0.34 to 2.16)	43 fewer per 1000 (from 201 fewer to 353 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events - 1g olsalazine vs. 2g sulphasalazine												
2	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	60/243 (24.7%)	46/243 (18.9%)	RR 1.3 (0.93 to 1.83)	57 more per 1000 (from 13 fewer to 157 more)	⊕⊕⊕⊕ LOW	IMPORTANT
Adverse events - 1.25g olsalazine vs. 2g sulphasalazine												
1	randomised trials	very serious <sup>3,4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	3/35 (8.6%)	4/40 (10%)	RR 0.86 (0.21 to 3.57)	14 fewer per 1000 (from 79 fewer to 257 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 2g olsalazine vs. 2g sulphasalazine												
1	randomised trials	serious <sup>3</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	6/34 (17.6%)	4/40 (10%)	RR 1.76 (0.54 to 5.74)	76 more per 1000 (from 46 fewer to 474 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 2g olsalazine vs. 4g sulphasalazine												
1	randomised trials	very serious <sup>1,4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	9/23 (39.1%)	8/23 (34.8%)	RR 1.13 (0.53 to 2.4)	42 more per 1000 (from 163 fewer to 487 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Serious adverse events - 1g olsalazine vs. 2g sulphasalazine												
1	randomised trials	serious <sup>6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,5</sup>	none	1/161 (0.62%)	0/161 (0%)	OR <sup>7</sup> 7.39 (0.15 to 372.38)	10 more per 1000 (from 10 fewer to 20 more) <sup>8</sup>	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Limited baseline characteristics.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>3</sup> Unclear method of allocation concealment.

<sup>4</sup> >10% difference in missing data between the treatment arms.

<sup>5</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>6</sup> Overall unclear method of randomisation and allocation concealment.

<sup>7</sup> Peto odds ratio.

<sup>8</sup> Risk difference has been calculated.

#### Additional information which could not be meta-analysed:

#### Relapse

The RIJK1992<sup>177</sup> paper did report a Kaplan Meier curve which showed the curves to overlap each other suggesting no significant difference between the two treatment groups.

The KIILERICH1992<sup>110</sup> paper reported a p value of 0.54 demonstrating no difference between 1g olsalazine and 2g sulphasalazine in terms of the cumulative relapse curves. A hazard ratio was not able to be calculated as it was based on ITT analysis and the n values could only be determined for the per-protocol analysis.

**Table 97: Oral ASAs versus oral ASAs (interclass comparison) – Mesalazine versus sulphasalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine	Sulphasalazine	Relative (95% CI)	Absolute		
Relapse (dichotomous) - 800mg-1.6g mesalazine versus 2-4g SASP												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	18/48 (37.5%)	17/44 (38.6%)	RR 0.97 (0.58 to 1.64)	12 fewer per 1000 (from 162 fewer to 247 more)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

#### Additional information which could not be meta-analysed:

#### Relapse

In the RILEY1988A<sup>178</sup> study, the Kaplan Meier curves crossed over each other demonstrating no significant difference between the mesalazine and sulphasalazine treatment groups in terms of relapse rates.

**Table 98: Oral ASAs versus oral ASAs (interclass comparison) – Balsalazide versus mesalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Balsalazide	Mesalazine	Relative (95% CI)	Absolute		
Relapse - 3g balsalazide versus 1.2g mesalazine												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	13/49 (26.5%)	16/46 (34.8%)	HR 0.74 (0.36 to 1.55)	77 fewer per 1000 (from 205 fewer to 137 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL

Relapse by 12 months (dichotomous) - 3g balsalazide versus 1.5g mesalazine												
1	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	13/48 (27.1%)	6/44 (13.6%)	RR 1.99 (0.83 to 4.77)	135 more per 1000 (from 23 fewer to 514 more)	⊕⊕⊕ LOW	CRITICAL
Relapse by 12 months (dichotomous) - 6g balsalazide versus 1.5g mesalazine												
1	randomised trials	very serious <sup>4,5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	3/40 (7.5%)	6/44 (13.6%)	RR 0.55 (0.15 to 2.05)	61 fewer per 1000 (from 116 fewer to 143 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events - 3.0g balsalazide vs. 1.2g mesalazine												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	30/49 (61.2%)	30/46 (65.2%)	RR 0.94 (0.69 to 1.28)	39 fewer per 1000 (from 202 fewer to 183 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 3.0g balsalazide vs. 1.5g mesalazine												
1	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	18/48 (37.5%)	20/44 (45.5%)	RR 0.82 (0.51 to 1.34)	82 fewer per 1000 (from 223 fewer to 155 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Adverse events - 6.0g balsalazide vs. 1.5g mesalazine												
1	randomised trials	very serious <sup>4,5</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	21/40 (52.5%)	20/44 (45.5%)	RR 1.16 (0.75 to 1.79)	73 more per 1000 (from 114 fewer to 359 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Serious adverse events - 3.0g balsalazide vs. 1.2g mesalazine												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	2/49 (4.1%)	3/46 (6.5%)	RR 0.63 (0.11 to 3.58)	24 fewer per 1000 (from 58 fewer to 168 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Limited baseline data (no information on extent of disease).

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>3</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>4</sup> Overall unclear method of randomisation and allocation concealment.

<sup>5</sup> >10% difference in missing data between the treatment arms.

**Table 99: Oral ASAs versus oral ASAs (interclass comparison) – Mesalazine (Asacol) versus mesalazine (Mezavant XL)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Asacol)	Mesalazine (Mezavant XL)	Relative (95% CI)	Absolute		
Relapse												
1	randomised	no serious	no serious	no serious	serious <sup>1</sup>	none	50/167	39/156	HR 1.16	34 more per 1000	⊕⊕⊕○	CRITICAL

	trials	risk of bias	inconsistency	indirectness			(29.9%)	(25%)	(0.77 to 1.77)	(from 51 fewer to 149 more)	MODERATE	
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Adverse events</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	99/169 (58.6%)	92/162 (56.8%)	RR 1.03 (0.86 to 1.24)	17 more per 1000 (from 80 fewer to 136 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
<b>Serious adverse events</b>												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1,2</sup>	none	5/169 (3%)	6/162 (3.7%)	RR 0.80 (0.25 to 2.57)	7 fewer per 1000 (from 28 fewer to 58 more)	⊕⊕○○ LOW	IMPORTANT

<sup>1</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

**Table 100: Oral ASAs versus oral ASAs (interclass comparison) – Mesalazine (Asacol) versus mesalazine (Pentasa)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mesalazine (Asacol)	Mesalazine (Pentasa)	Relative (95% CI)	Absolute		
Relapse												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	13/65 (20%)	13/64 (20.3%)	HR 0.90 (0.42 to 1.94)	18 fewer per 1000 (from 112 fewer to 153 more)	⊕⊕○○ LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/65 (95.4%)	62/65 (95.4%)	RR 1.00 (0.93 to 1.08)	0 fewer per 1000 (from 67 fewer to 76 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Serious adverse events												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	2/65 (3.1%)	1/65 (1.5%)	RR 2.00 (0.19 to 21.52)	15 more per 1000 (from 12 fewer to 316 more)	⊕⊕○○ LOW	IMPORTANT

<sup>1</sup> Crosses both the lower (0.75) and upper (1.25) relative risk (RR) MIDs.

**Table 101: Oral ASAs versus oral ASAs (regimen comparison) – Once a day versus more than once a day**

Quality assessment							No of patients		Effect		Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Once a day	More than once a day	Relative (95% CI)	Absolute		
<b>Relapse</b>												
3	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	128/694 (18.4%)	160/710 (22.5%)	HR 0.80 (0.63 to 1.01)	41 fewer per 1000 (from 77 fewer to 2 more)	⊕⊕⊕ LOW	CRITICAL
<b>Relapse (dichotomous) - At 6 months</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	1/12 (8.3%)	1/10 (10%)	RR 0.83 (0.06 to 11.7)	17 fewer per 1000 (from 94 fewer to 1000 more)	⊕⊕⊕ VERY LOW	CRITICAL
<b>Relapse (dichotomous) - At 1 year</b>												
3	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	69/395 (17.5%)	48/417 (11.5%)	RR 1.45 (1.04 to 2.03)	52 more per 1000 (from 5 more to 119 more)	⊕⊕⊕ LOW	CRITICAL
<b>Quality of life</b>												
0	No evidence available					none	-	-	-	-		CRITICAL
<b>Adverse events</b>												
4	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	328/715 (45.9%)	307/749 (41%)	RR 1.12 (1 to 1.26)	49 more per 1000 (from 0 more to 107 more)	⊕⊕⊕ LOW	IMPORTANT
<b>Serious adverse events</b>												
5	randomised trials	serious <sup>4</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	47/1227 (3.8%)	30/1260 (2.4%)	RR 1.61 (1.03 to 2.53)	15 more per 1000 (from 1 more to 36 more)	⊕⊕⊕ LOW	IMPORTANT

<sup>1</sup> Single blind.

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>3</sup> Crosses the upper (1.25) relative risk (RR) MID.

<sup>4</sup> Single blind and open studies. One double blind, but no further information was given.

#### Additional information which could not be meta-analysed:

#### Relapse

In the DIGNASS2009<sup>58</sup> study, the median time to relapse was also reported which was 202.0 days and 148.0 days (log rank test p=0.08) in the once a day and twice a day regimens respectively.

**Table 102: Oral ASAs versus oral ASAs (regimen and dose comparison)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose once a day	Lower dose twice a day	Relative (95% CI)	Absolute		

Relapse												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	51/415 (12.3%)	57/411 (13.9%)	HR 0.89 (0.6 to 1.31)	13 fewer per 1000 (from 48 fewer to 35 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Serious adverse events												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2,3</sup>	none	6/415 (1.4%)	3/411 (0.73%)	RR 1.98 (0.5 to 7.87)	7 more per 1000 (from 4 fewer to 50 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Very limited baseline characteristics. No baseline extent data, when extent of disease was specified as a subgroup (data not reported). Stated to be double blind but no further information was given.

<sup>2</sup> Crosses the upper 1.25 relative risk (RR) MID.

<sup>3</sup> Crosses the lower 0.75 relative risk (RR) MID.

**Table 103: Oral ASAs versus oral ASAs (regimen comparison) – Continuous versus intermittent oral ASAs**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous treatment	Intermittent treatment	Relative (95% CI)	Absolute		
Relapse (continuous versus intermittent) - 1.6g oral 5-ASA once a day versus 2.4g 5-ASA for 1st 7 days of each month												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	8/23 (34.8%)	7/24 (29.2%)	HR 1.35 (0.49 to 3.73)	81 more per 1000 (from 136 fewer to 432 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Limited baseline characteristics. Open study.

<sup>2</sup> Crosses the lower (0.75) and upper (1.25) relative risk (RR) MIDs

## 7.13 Economic evidence

### Published literature

Two studies<sup>40,230</sup> were included with the relevant comparison. These are summarised in the economic evidence profile below. See also the study selection flow chart in Appendix E and study evidence tables in Appendix G.

One study<sup>186</sup> that met the inclusion criteria was selectively excluded due to the availability of a similar study with greater applicability. See Appendix F for list of excluded studies, with reasons for exclusion given.

**Table 104: Economic evidence profile: oral ASA**

Study	Limitations	Applicability	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
<b>No maintenance 5-ASA versus 2.4g/day mesalazine maintenance</b>							
Yen <sup>230</sup>	Minor limitations	Partially applicable <sup>(a)</sup>	5-ASA clinical probabilities were based on weighted average results from RCTs that assessed different 5-ASAs.	£2,938 <sup>(b)</sup>	0.02 QALYs	£146,000/QALY <sup>(b)</sup>	<p>One-way sensitivity analysis was undertaken on all the input parameters. Two input variables that impacted on the ICER was the relative risk of flare on maintenance 5-ASA and cost of 5-ASA.</p> <p>If the cost of 5-ASA was £9/month (sulfasalazine), the ICER was estimated to be £10,306/QALY.<sup>(b)</sup></p>
<b>2g once daily (OD) mesalazine versus 1g twice daily (BD) mesalazine</b>							
Connolly <sup>40</sup>	Minor limitations	Directly applicable	Relative treatment effect was obtained from one study.	-£156	0.004 QALYs	2g OD mesalazine dominates (less costly and more effective)	Probability of 2g OD mesalazine being cost-effective around a £20,000 threshold was 98%.

(a) The cost-effectiveness model was designed to reflect the management of ulcerative colitis in the US therefore resource use may not be applicable to the UK health system. Some health state utilities were inferred from a Crohn's disease population.

(b) Costs were converted from US dollars to UK pounds using Purchasing Power Parities<sup>161</sup>



The studies addressed issues that the GDG considered relevant when considering treatment options for maintenance of remission. However, not all the clinical evidence addressed in the clinical review section was used in these studies. In addition, the GDG considered that clarification on the use of a high or low maintenance dose of aminosalicylate after a flare of disease would be useful. This has not been captured in the studies.

### **New cost-effectiveness analysis**

Note that this area was prioritised for new cost-effectiveness analysis. This will look at the most cost-effective treatment for maintenance of remission.

## **7.14 Evidence statements**

### **7.14.1 Clinical evidence statements**

#### **7.14.1.1 Oral ASAs versus placebo**

##### **Relapse**

Oral ASAs are clinically more effective in reducing relapse rates compared to placebo [Low quality evidence, 4 studies, N=536]

##### **Important outcomes**

There may be no clinical difference between oral ASAs and placebo for adverse events, serious adverse event or hospitalisations [very low quality evidence 3 studies, N=339;1 study, N=174;1 study, N=200]

#### **7.14.1.2 Oral ASAs versus oral ASAs (dose comparison)**

##### **Asacol**

##### **Relapse**

There may be no clinical difference between 1.2g and 2.4g of mesalazine (Asacol) in reducing relapse rates by 12 months or for those with more than 3 relapses per year or for those people with less than or equal to 3 relapses per year [very low quality evidence, 1 study, N=156;1 study, N=1041 study; N=52]

##### **Important outcomes**

There may be no clinical difference between 1.2g and 2.4g of mesalazine (Asacol) for adverse event rates [very low quality evidence,1 study, N=156]

##### **Salofalk**

##### **Relapse**

3.0g of mesalazine (Salofalk) is clinically more effective in reducing relapse rates compared to 1.5g [High quality evidence, 1 study, N=429]

##### **Adverse events**

3.0g of mesalazine (Salofalk) may have lower adverse event rates compared to 1.5g but there may be no difference in serious adverse events [Low to moderate quality evidence, 1 study, N=429]

##### **Olsalazine**

### **Relapse**

2.0g of olsalazine may be clinically more effective in reducing relapse rates compared to 1.25g by 6 months and 1g at 12 months [Low quality evidence ,1 study, N=69, 1 study N=127]

### **Adverse events**

There may be no clinical difference in adverse event rates between 1.25g and 2.0g of olsalazine at 6 months and 1.0g of olsalazine may have a lower adverse event rate compared to 2.0g at 12 months [Very low quality evidence ,1 study, N=69, 1 study, N=108]

### **Sulphasalazine**

#### **Relapse**

There may be no clinical difference in reducing relapse rates between 2g and 4g of sulphasalazine [very low quality evidence ,1 study, N=113]

### **Balsalazide**

#### **Relapse**

6g of balsalazide may be clinically more effective in reducing relapse rates compared to 3g by 26 weeks but there may be no clinical difference by 12 months [low quality evidence,1 study, N=88, 1 study, N=108]

### **Adverse events**

3g of balsalazide may have a lower adverse event rate compared to 6g [very low quality evidence,1 study, N=88]

## **7.14.1.3 Oral ASAs versus oral ASAs (interclass comparison)**

### **Olsalazine versus mesalazine**

#### **Relapse**

1g of olsalazine may be clinically more effective in reducing relapse rates compared to 1.2g mesalazine (Asacol) [Low quality evidence 1 study, N=99]

### **Olsalazine versus sulphasalazine**

#### **Relapse**

There may be no clinical difference in reducing relapse rates between 1g or 1.25g olsalazine versus 2g sulphasalazine [very low to moderate quality evidence, 1 study, N=486; 1 study ,N=486;1 study, N=197;1 study, N=75], 2g olsalazine may be clinically more effective in reducing relapse rates compared to 2g sulphasalazine [ very low quality evidence ,1 study, N=74] but there may be no clinical difference in reducing relapse rates between 2g olsalazine and 4g sulphasalazine [ very low quality evidence,1 study, N=46]

### **Adverse events**

There may be no clinical difference in adverse event rates between 1g or 1.25g of olsalazine and 2g sulphasalazine, 2g olsalazine and 2g or 4g of sulphasalazine [Low and very low quality evidence,1 study, N=486, 1 study, N=75, 1 study, N=74, 1 study, N=46]. There may be no clinical difference in serious adverse event rates between 1g olsalazine and 2g sulphasalazine [very low quality evidence 1 study, N=322]

### **Mesalazine versus sulphasalazine**

#### **Relapse**

There may be no clinical difference in reducing relapse rates between 800-1.6g mesalazine (unknown type) versus 2-4g sulphasalazine [Low quality evidence 1 study, N=92]

#### **Balsalazide versus mesalazine**

There may be no clinical difference in reducing relapse rates between 3g balsalazide and 1.2g mesalazine (Asacol) [very low quality evidence, 1 study, N=95], 1.5g mesalazine (Salofalk) may be clinically more effective in reducing relapse rates compared to 3g balsalazide [Low quality evidence 1 study, N=92] , there may be no clinical difference in reducing relapse rates between 6g balsalazide and 1.5g mesalazine (Salofalk) [very low quality evidence 1 study, N=84]

#### **Adverse events**

There may be no clinical difference in adverse event rates between 3g balsalazide and 1.2g or 1.5g mesalazine (Asacol and Salofalk respectively), 6g balsalazide or 1.5g mesalazine (Salofalk) or in serious adverse events between 3g balsalazide and 1.2g mesalazine (Asacol) [very low quality evidence 1 study, N=95; 1 study, N=92; 1 study; N=84;1 study, N=95, ]

#### **Mesalazine (Asacol) versus mesalazine (Mezavant XL)**

##### **Relapse**

There may be no clinical difference at reducing relapse rates between 2.4g mesalazine (Asacol) and 2.4g mesalazine (Mezavant XL) [ Moderate quality evidence1 study, N=323]

##### **Adverse events**

There may be no clinical difference in adverse or serious adverse event rates between 2.4g mesalazine (Asacol) and 2.4g mesalazine (Mezavant XL) [ High quality evidence to low quality evidence,1 study, N=331]

#### **Mesalazine (Asacol) versus mesalazine (Pentasa)**

##### **Relapse**

There may be no clinical difference at reducing relapse rates between 2.4g mesalazine (Asacol) and 2.25g mesalazine (Pentasa) [low quality evidence,1 study, N=129]

##### **Adverse events**

There may be no clinical difference in adverse or serious adverse event rates between 2.4g mesalazine (Asacol) and 2.25g mesalazine (Pentasa) [high quality evidence,1 study, N=130]

#### **7.14.1.4 Oral ASAs versus oral ASAs (regimen comparison) – once a day versus more than once a day**

##### **Relapse**

Low quality evidence showed there may be no clinical difference in reducing relapse rates between once a day and more than once a day treatment regimens at 6 or 12 months [very low to low quality evidence ,3 studies, N=1304; 1 study, N=22; 3 studies, N=802]

##### **Adverse events**

There may be a clinical difference in adverse or serious adverse event rates between once a day and more than once a day [low quality evidence, 4 studies, N=1464;5 studies, N=2487]

#### **7.14.1.5 Oral ASAs versus oral ASAs (regimen and dose comparison)**

##### **Relapse**

There may be no clinical difference in reducing relapse rates between 2.4g mesalazine (Mezavant XL) once a day and 1.6g mesalazine (Asacol) given as 800mg twice a day [very low quality evidence, 1 study, N=826]

#### **Serious adverse events**

There may be no clinical difference in serious adverse event rates between 2.4g mesalazine (Mezavant XL) once a day and 1.6g mesalazine (Asacol) given as 800mg twice a day [very low quality evidence, 1 study, N=826]

### **7.14.1.6 Oral ASAs versus oral ASAs (regimen comparison) – continuous versus intermittent oral ASAs**

#### **Relapse**

There may be no clinical difference in reducing relapse rates between 1.6g 5-ASA (type not specified) once a day and 2.4g 5-ASA (type not specified) for the first seven days of each month [very low quality evidence, 1 study, N=47]

### **7.14.2 Economic evidence statements**

One partially applicable economic study with minor limitations found that in comparison to no maintenance, maintenance treatment with 5-ASA costs more and yields better outcomes with the ICER being £146,000/QALY.

One directly applicable economic study with minor limitations found that in comparison to 1g twice daily mesalazine, maintenance treatment with 2g once daily mesalazine costs less and yields better outcomes.

## **7.15 Clinical evidence: Combinations of treatments**

Five studies were included in the review.<sup>3,46,48,133,231</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.

## 7.16 Evidence profile

### 7.16.1 Continuous oral aminosalicylates versus intermittent topical aminosalicylates

Table 105: Continuous oral aminosalicylates versus intermittent topical aminosalicylates

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral ASAs	Intermittent topical ASAs	Relative (95% CI)	Absolute		
Relapse												
2	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/34 (55.9%)	9/35 (25.7%)	HR 3.57 (1.6 to 7.93)	397 more per 1000 (from 121 more to 648 more)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	2/31 (6.5%)	0/29 (0%)	OR <sup>3</sup> 7.16 (0.44 to 117.45)	60 more per 1000 (from 40 fewer to 170 more) <sup>4</sup>	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Colectomy												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/19 (5.3%)	0/19 (0%)	OR <sup>3</sup> 7.39 (0.15 to 372.38)	50 more per 1000 (from 80 fewer to 190 more) <sup>4</sup>	⊕⊕⊕⊕ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Single blind.

<sup>2</sup> Crosses the lower (0.75) and upper (1.25) relative risk (RR) MIDs.

<sup>3</sup> Peto odds ratio.

<sup>4</sup> The absolute effect has been calculated from the risk differences.

#### Additional data which could not be meta-analysed:

##### Relapse

In the DALBASIO1990<sup>48</sup> study (N=60)3 the log rank p value is reported as >0.05. As it was not an exact p value a hazard ratio was unable to be calculated. The actuarial Kaplan Meier curves cross over each other several times. 2g oral SASP does not appear to have a significantly different relapse rate compared to 4g topical 5-ASA given daily for the first 7 days of each month for patients with proctosigmoiditis and proctitis.

## Adverse events

The ANDREOLI1994<sup>3</sup> study (N=31)1 comparing 2g oral SASP to biweekly 5-ASA enemas found that no patients had significant side effects on either treatment. The same was found in the MANTZARIS1994<sup>133</sup> study (N=38)4 comparing 1.5g mesalazine (Salofalk) and 4g mesalazine (Salofalk) enema (every third night).

**Table 106: Continuous oral ASAs & intermittent topical ASAs versus continuous oral ASAs**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous oral ASAs & intermittent topical ASAs	Continuous oral ASAs	Relative (95% CI)	Absolute		
Relapse												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/47 (31.9%)	33/49 (67.3%)	HR 0.39 (0.21 to 0.72)	320 fewer per 1000 (from 120 fewer to 464 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup>Unclear method of randomisation, open study.

## Additional data which could not be meta-analysed:

## Adverse events

In both studies (DALBASIO1997<sup>46</sup> & YOKOYAMA2007<sup>231</sup>, N=96)2,5 comparing oral 5-ASA and twice weekly 5-ASA enemas to oral 5-ASA alone, there were no drug related adverse events reported in either treatment group.

## 7.17 Economic evidence

### Published literature

Two studies<sup>46,164</sup> were included with the relevant comparison. These are summarised in the economic evidence profile below. See also the study selection flow chart in Appendix E and study evidence tables in Appendix G.

No studies that met the inclusion criteria were selectively excluded.

**Table 107: Economic evidence profile: Continuous oral ASA and intermittent topical ASA versus continuous oral ASA**

Study	Limitations	Applicability	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Piodi <sup>164</sup>	Very serious limitations <sup>(a)</sup>	Partially applicable <sup>(b)</sup>	Estimate of treatment effects obtained from one source (case control study, small sample size).	£186 <sup>(c)</sup>	0.20 relapses avoided	£929 per relapse avoided <sup>(c)</sup>	Sensitivity analysis not reported
d'Albasio <sup>46</sup>	Very serious limitations <sup>(a)</sup>	Partially applicable <sup>(b)</sup>	Within-trial analysis so estimate of treatment effects obtained from one source.	£300.07 <sup>(c)</sup>	0.3 relapses avoided	£1000.25 per relapse avoided <sup>(c)</sup>	Sensitivity analysis not reported

(a) Limited information provided on resource use. Costs sources and calculations not clearly reported. No sensitivity analysis conducted.

(b) The study was designed to reflect the management of ulcerative colitis in the Italy therefore resource use may not be applicable to the UK health system. The value of health effects were not expressed in terms of quality-adjusted life years.

(c) Costs were converted from US dollars to UK pounds using Purchasing Power Parities<sup>161</sup>



### **New cost-effectiveness analysis**

New analysis was not prioritised for this area.

### **Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

## **7.18 Evidence statements**

### **7.18.1 Clinical evidence statements**

#### **7.18.1.1 Continuous oral ASAs versus intermittent rectal ASAs**

##### **Relapse**

Intermittent topical ASAs are clinically more effective in reducing relapse rates compared to oral ASAs [low quality evidence, 2 studies, N=69]

##### **Adverse events**

There may be no clinical difference between continuous oral ASAs and intermittent topical ASAs in adverse event or colectomy rates [very low quality evidence 1 study, N=60; 1 study, N=38]

#### **7.18.1.2 Continuous oral ASAs & intermittent topical ASAs versus continuous oral ASAs**

##### **Relapse**

Continuous oral ASAs and intermittent topical ASAs to be clinically more effective in reducing relapse rates compared to oral ASAs alone [moderate quality evidence, 2 studies, N=96]

### **7.18.2 Economic evidence statements**

Two partially applicable economic studies with very serious limitations found that in comparison to oral 5-ASA treatment, maintenance treatment with continuous oral and intermittent topical 5-ASA costs more but reduces the frequency of relapse.

## **7.19 Network meta-analysis**

Two NMAs were performed; a baseline NMA which compared all treatments and a combined NMA which addressed the relationship between low and high doses of aminosalicylates. The combined NMA informed the inputs in the original health economic models which are described in Appendix L. For detailed explanation on methodology and results of NMAs refer to Appendix J.

### **7.19.1 Comparison of the maintenance of remission treatments (baseline NMA)**

A NMA was performed to compare the treatments for the maintenance of remission in people with left-sided/extensive ulcerative colitis. The analyses were based on a total of 18 studies. These studies formed two networks of evidence for the outcomes: rate of relapse and number of withdrawals. The number of withdrawals rather than withdrawals due to treatment specific adverse events was

chosen due to unclear reporting in the trials. These outcomes were considered by the GDG as the most important clinical outcomes. The interventions included in each network are shown in Table 108. For more details on the network please see Appendix J.

**Table 108: Maintenance of remission treatments included in the network meta-analyses of people in remission with ulcerative colitis**

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

### 7.19.2 Evidence summary

#### Relapse

A NMA of 18 studies comparing 12 treatments suggested all the treatments were better than placebo. The low and high doses of olsalazine and low and high doses of sulfasalazine are significantly better than placebo. With the overlapping confidence intervals of the different treatments it is difficult to be confident of one treatment's superiority compared to the alternative treatments for the maintenance of remission compared to placebo.

#### Withdrawals

A NMA of 13 studies comparing 12 treatments suggested that there was no significant difference in withdrawal from treatments.

### 7.19.3 Comparison of the maintenance of remission treatments with the aminosaliclates combined into low and high doses (combined NMA)

A NMA combining the aminosaliclates was performed following the results of the baseline NMA to look at the relationship between placebo, low and high dose aminosaliclates. The analysis informed the inputs into the original health economic model.

The analyses were based on a total of 13 studies. These studies formed two networks of evidence for the two outcomes: rate of relapse and number of withdrawals. The interventions included in each network are shown in Table 109. For more details on the network please see appendix I.

**Table 109: Maintenance of remission treatments (combined aminosaliclates) included in the network meta-analyses of people in remission with ulcerative colitis**

Combined Network Meta-Analysis	
Network 1: Relapse	Network 2: Withdrawals
Placebo	Placebo

Combined Network Meta-Analysis	
Network 1: Relapse	Network 2: Withdrawals
Low dose ASA	Low dose ASA
High dose ASA	High dose ASA

## 7.19.4 Evidence summary

### Relapse

A NMA of 13 studies comparing 3 treatments suggested that high dose ASA and low dose ASA were more effective than placebo at maintaining remission. High dose ASA was shown to be better than low dose ASA although there was an overlap between the confidence intervals.

### Withdrawal

A NMA of 13 studies comparing 3 treatments suggested there was a higher probability of withdrawing from low dose ASA than from high dose ASA.

## 7.20 Health economic maintenance model summary

### 7.20.1 Original economic analysis

The GDG considered the available evidence on cost-effectiveness of aminosalicylates in maintaining remission. A study by Yen<sup>230</sup> assessed the cost-effectiveness of no maintenance therapy versus 5-ASA maintenance therapy in patients with mild to moderate UC. 5-ASA therapy was shown to increase the discounted QALYs per person yielding an incremental cost-effectiveness ratio (ICER) of £146,000/QALY. This figure was highly dependent on the daily cost of ASAs as a sensitivity analysis showed that the ICER was £10,306/QALY when cheaper drug costs of sulfasalazine were used. The GDG noted that there were issues surrounding the applicability of this study as some health state utilities were inferred from a Crohn's disease and the model was based on a non-UK population. The network meta-analysis (described in Appendix I) conducted on oral ASA maintenance treatments provided effectiveness data for low dose oral ASAs and high dose oral ASAs. The GDG felt that majority of patients would be on maintenance therapy after successful induction of remission and therefore considered this topic to be a top priority for original economic analysis. Hence, the original economic model presented here sought to address the question about the cost-effectiveness of different doses of ASAs for maintaining remission in people with ulcerative colitis. A summary of the analysis is presented below and a full description can be found in Appendix L.

### 7.20.2 Methods

#### 7.20.2.1 Model overview

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services (PSS) perspective. A Markov model was constructed in order to estimate the costs and QALYs associated with different treatment strategies for the maintenance of remission. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance<sup>151</sup>. Uncertainty was explored through probabilistic and sensitivity analyses. The time horizon considered in the base case model was 2 years. This time horizon was chosen to reflect the duration of the longest trial explored in the clinical review for maintenance of remission.

### 7.20.2.2 Population

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

### 7.20.2.3 Comparators

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

A second NMA (combined NMA) was therefore conducted which combined trials reporting low dose oral ASAs into one treatment group, and trials reporting high dose oral ASAs into another treatment group. The results of this NMA informed the clinical inputs in this economic analysis.

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

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

### 7.20.2.4 Model structure

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

Treatment effects in this economic model were based on these two outcomes - withdrawals and relapses.

A cycle length of two months was chosen to reflect the duration of the treatment of patients who are undergoing induction treatment for a flare. In any 2-month cycle, patients could remain in remission or experience a relapse. Patients who experienced a relapse were treated with the cost-effective

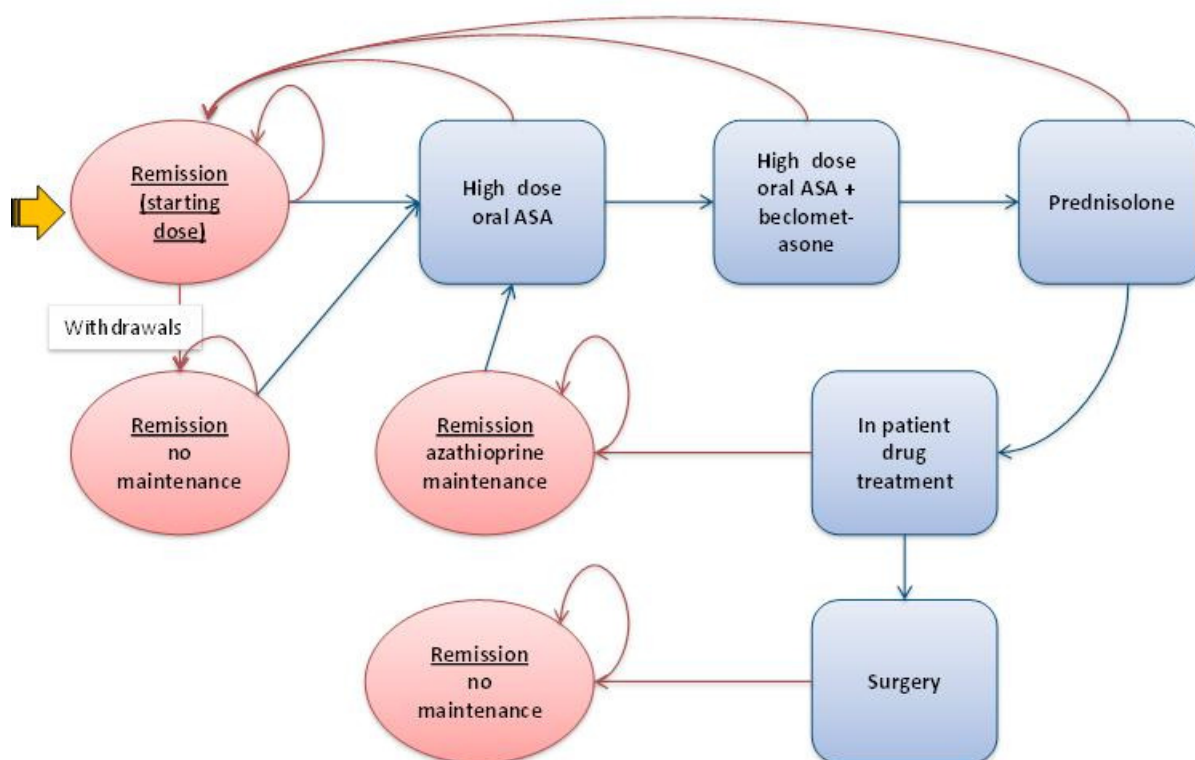
treatment strategy derived from the induction of remission economic model. The strategy involved outpatient treatment with a high induction dose of oral ASA. In the event of failure to respond to this therapy, treatment was escalated as follows: high induction dose of oral ASA + beclometasone, followed by prednisolone. If the flare persisted, patients were treated as inpatients and received intravenous drug therapy which could be with either steroids or ciclosporin. Finally, lack of response to intravenous therapy resulted in patients having surgery.

There were three options modelled for patients who went into remission after an outpatient flare. They could receive no treatment or they could be placed on either a low dose oral ASA or high dose oral ASA maintenance therapy. Inpatients that went into drug-induced remission were placed on azathioprine maintenance therapy while inpatients that had surgically-induced remission remained in remission for the rest of the model and were not on any maintenance treatment. All patients in remission (except surgical remission) had a probability of relapsing.

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

The first model structure shown in Figure 5 is relevant for comparators 1, 4 and 6 as described above. Based on this, patients entered the model on one of the following options - no maintenance, low dose oral ASA or high dose oral ASA. In the event of a flare, they were treated as described above and following remission, they returned to the same maintenance regimen with which they entered the model.

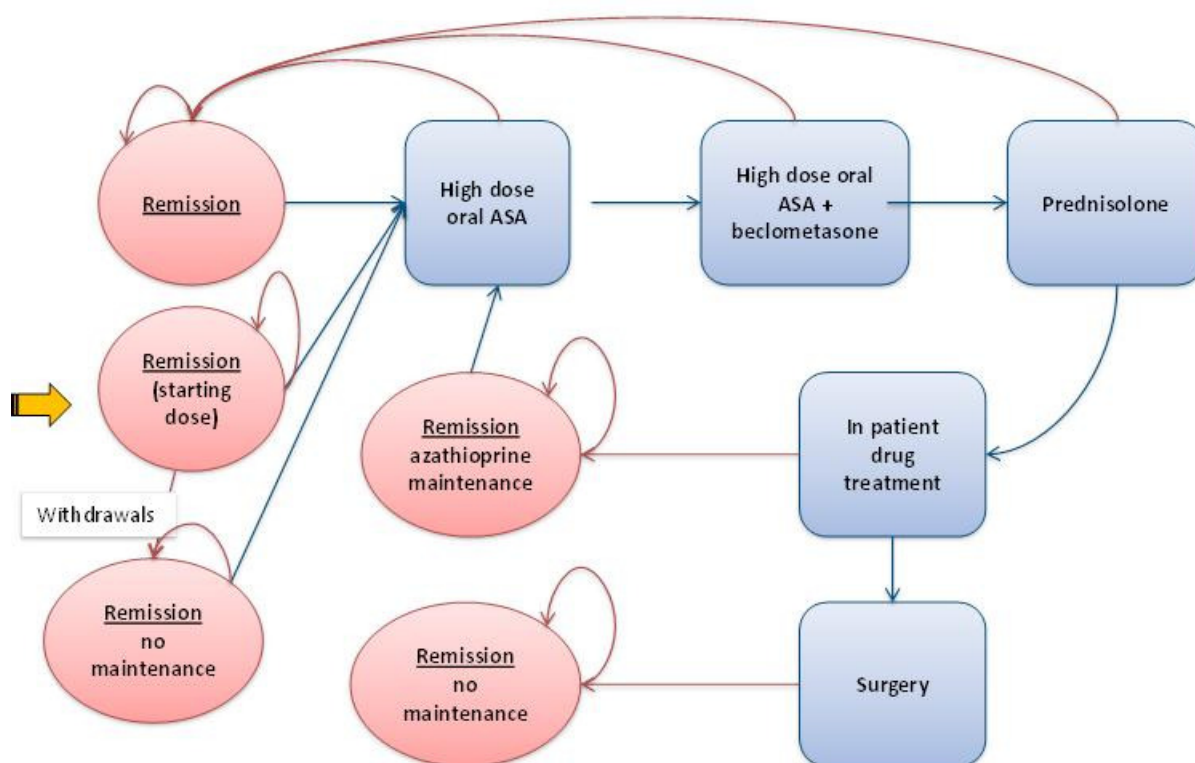
**Figure 5: Markov model structure for comparators 1, 4 and 6**



The second model structure shown in Figure 6 is relevant for comparators 2, 3 and 5 as described above. Based on this, patients entered the model on either no maintenance or low dose oral ASA. In

the event of a flare, they were treated as described above but returned to a maintenance regimen different to that with which they entered the model.

**Figure 6: Markov model structure for comparators 2, 3 and 5**



#### 7.20.2.5 Model inputs

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs were validated by the GDG.

#### 7.20.2.6 Sensitivity analysis

In total, five uni-variate sensitivity analyses were conducted, whereby, for each analysis one key model input was changed in order to explore the sensitivity of model results to changes in that parameter. One multi-variate sensitivity analysis was conducted deterministically to address the effects of ASA costs on the model results.

A probabilistic analysis was carried out whereby distributions were assigned to treatment effects, utilities and, where possible, costs in order to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.

### 7.20.3 Results

#### 7.20.3.1 Base case

The results showed that the cost-effective option is the low maintenance returning to low maintenance strategy as it yields the highest net monetary benefit (NMB). This strategy involves

starting patients on low maintenance dose ASA and returning to a low maintenance dose ASA after treating an outpatient flare.

Table 110 shows the breakdown of the results. The low maintenance returning to low maintenance strategy had the highest NMB and was cost-effective in 61% of the simulations. The high maintenance returning to high maintenance strategy was cost-effective in 30% of cases. This shows that while the low maintenance returning to low maintenance strategy is likely to be cost-effective there is uncertainty about this result and there is a good possibility that high maintenance returning to high maintenance strategy could be cost-effective.

**Table 110: Cost-effectiveness in the base case (per patient)**

Comparator	Costs	QALYs	NMB <sup>(a)</sup>	NMB rank (95% confidence interval) <sup>(a)</sup>	Probability of being most cost-effective strategy	ICER compared to no maintenance
No maintenance returning to no maintenance strategy	£926	1.780	£34,670	5(1,6)	9%	comparator
No maintenance returning to low dose oral ASA strategy	£1,011	1.787	£34,720	4(2,6)	0%	£12,526
No maintenance returning to high dose oral ASA strategy	£1,165	1.789	£34,618	6(2,6)	0%	£25,596
Low dose oral ASA returning to low dose oral ASA strategy	£1,041	1.798	£34,916	1(1,6)	61%	£6,382
Low dose oral ASA returning to high dose oral ASA strategy	£1,157	1.800	£34,839	2(2,5)	0%	£11,534
High dose oral ASA returning to high dose oral ASA strategy	£1,356	1.805	£34,749	3(1,6)	30%	£16,909

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

One-way sensitivity analyses were conducted in order to test the robustness of model results. Over a 5 year time horizon, the low dose oral ASA returning to low dose oral ASA strategy remained the cost-effective option. This was also the same result when the impact of a 1.5% QALY discount rate on the analysis was assessed.

A sensitivity analysis was conducted using a higher baseline risk which suggests that patients are more likely to have a relapse. In this scenario, the high dose oral ASA returning to high dose oral ASA strategy was the cost-effective option. This can be interpreted to mean that it is cost-effective to maintain patients who are more prone to relapses on a high dose ASA due to it being more efficacious than other comparators. Cost gains are made by preventing downstream costs of more expensive drug treatment and hospitalisations. The same analysis was conducted but with a lower baseline risk suggesting that patients are less prone to relapses. In this scenario, the no maintenance returning to no maintenance strategy was the cost-effective option. This means that for patients who do not frequently relapse, it is cost-effective to treat them only when they have a flare. SA5, which

addressed the uncertainty in withdrawal rates did not change the conclusions of the base case analysis.

#### **7.20.4 Discussion**

##### **7.20.4.1 Limitations and interpretation**

- The costs and dis-utilities of drug-specific adverse events were not explicitly modelled due to lack of robust data. This means that the cost-effectiveness of oral ASAs may have been over-estimated although the magnitude is unknown as each individual ASA is likely to have a specific side-effect profile. The overestimation of the ICER would be greater for ASAs that have more serious side effects compared to those with less serious side effects. This introduces uncertainty around interpretation of the results.
- In the model, it is assumed that all relapses have the same severity. It is possible therefore that the induction treatment sequence may not be appropriate for all patients. This assumption may over estimate the cost-effectiveness of all comparators.
- Mesalazines, such as Mesren and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment about the relative efficacy of these mesalazines hence caution should be exercised when generalising the results of this model.
- Patients who withdraw from treatment were assumed to still be in remission. This is a conservative approach. If withdrawal from treatment results in flare of disease, the cost-effectiveness of all comparators may have been overestimated in the model.
- Treatment adherence was assumed to be 100% in the model. The GDG however noted that this may not be the case in reality and measures to improve adherence are discussed elsewhere in the guideline.

##### **7.20.4.2 Generalisability to other populations/settings**

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

Relapses in the model are assumed to be mild to moderate initially. In reality, patients may experience greater severities of relapse which may necessitate treatment options different to those captured in the model. Similarly, other extents of ulcerative colitis such as proctitis have not been addressed and as such treatment options used in the model may not be applicable.

#### **7.20.5 Conclusion/evidence statement**

The original cost-effectiveness analysis conducted for this guideline suggests that low dose oral ASA is the most cost-effective option to maintain remission in patients with left sided or extensive ulcerative colitis, although there is considerable uncertainty related to interpretation of the withdrawals data.

## **7.21 Clinical evidence: Immunomodulators**

Eight studies were included in the review.<sup>91,103,134,140,160,204-206</sup> Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix F.



As per the review protocol, studies where the randomisation occurred with the patients in remission have been included. As immunomodulators are often started in addition to corticosteroids for the induction of remission to allow the tapering of corticosteroids and their continuation as a maintenance treatment, studies that have used this treatment regimen and randomised the patients at the point of induction have also been included but analysed separately. There is a risk of bias associated with this method due to not all of the patient's entering remission or taking different times to enter remission and this has been taken into account when interpreting the results of these studies. For these studies, relapse figures are calculated as those who relapse after having remission induced. The other outcomes are reported over the whole trial period e.g. adverse events.

There were only 2 studies identified that matched our inclusion criteria which looked at the use of azathioprine for the maintenance of remission. The other 6 studies were randomised at the point of the induction of remission.

"Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis" was published by the Cochrane collaboration in 2007 and was updated in 2012<sup>209</sup>. New studies that were identified in the search were excluded. The review included 6 studies which looked at the following comparisons:

- Azathioprine versus placebo
- Azathioprine versus 6-mercaptopurine
- 6-mercaptopurine versus methotrexate

The Cochrane review concluded that azathioprine is clinically more effective at maintaining remission compared to placebo, and that azathioprine or 6-mercaptopurine could be used for maintenance treatment in people who have failed or cannot tolerate mesalazine or sulphasalazine and for those who require repeated courses of corticosteroids. The Cochrane review was excluded because it differed from the clinical review protocol in terms of the methods of analysis; the clinical review used hazard ratios in preference to relative risk ratios to take account of the time horizon and studies where the patients are randomised at the point of induction are separated from those in which patients have been in remission for a period of time. Combinations of azathioprine and an aminosalicylates were also not included in the Cochrane review. However, all of the studies included in the Cochrane review appear in the clinical review.

"Methotrexate for maintenance of remission in ulcerative colitis" was published by the Cochrane collaboration in 2009 and has since been updated in 2010<sup>61</sup>. The review only included one study which looked at methotrexate (12.5mg) versus placebo. The Cochrane review concluded that there was insufficient evidence to recommend the use of methotrexate to maintain remission in patients with ulcerative colitis. Although the Cochrane review has been excluded as it did not report relapse as an outcome, only maintenance of remission, the same study has been included in the clinical review.

## 7.22 Evidence profile

### 7.22.1 Azathioprine versus placebo

Table 111: Azathioprine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine	Placebo	Relative (95% CI)	Absolute		
Relapse												
2	randomised trials	very serious <sup>1,2,3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	16/50 (32%)	30/52 (57.7%)	HR 0.42 (0.23 to 0.77)	274 fewer per 1000 (from 93 fewer to 397 fewer)	⊕○○○ VERY LOW	CRITICAL
Relapse - Randomised when in remission												
1	randomised trials	serious <sup>1,3</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	12/33 (36.4%)	20/34 (58.8%)	HR 0.47 (0.23 to 0.96)	247 fewer per 1000 (from 15 fewer to 404 fewer)	⊕⊕○○ LOW	CRITICAL
Relapse - Randomised with active disease												
1	randomised trials	very serious <sup>1,2</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	4/17 (23.5%)	10/18 (55.6%)	HR 0.31 (0.1 to 1)	333 fewer per 1000 (from 478 fewer to 0 more)	⊕○○○ VERY LOW	CRITICAL
Relapse rate at 1 year - Randomised with active disease												
2	randomised trials	very serious <sup>1,2,5,6</sup>	no serious inconsistency	no serious indirectness	serious <sup>4</sup>	none	24/62 (38.7%)	30/58 (51.7%)	RR 0.73 (0.51 to 1.04)	140 fewer per 1000 (from 253 fewer to 21 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events												
2	randomised trials	very serious <sup>1,2,5,6</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4,7</sup>	none	7/65 (10.8%)	3/65 (4.6%)	RR 2.14 (0.63 to 7.3)	53 more per 1000 (from 17 fewer to 291 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment.

<sup>2</sup> Randomised at induction of remission.

<sup>3</sup> Stated to be double blind, but no further information was given.

<sup>4</sup> Crosses the lower (0.75) relative risk (RR) MID.

<sup>5</sup> Unclear blinding.

<sup>6</sup> One study had significant differences in duration of disease between the two groups at study entry.

<sup>7</sup> Crosses the upper (1.25) relative risk (RR) MID.

### Additional information which could not be meta-analysed:

**Adverse events:** In the SOOD2002A<sup>204</sup> study of azathioprine, sulphasalazine and steroids versus placebo, sulphasalazine and steroids, there were no adverse events reported in either treatment arm.

**Table 112: Azathioprine versus sulphasalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine	Sulphasalazine	Relative (95% CI)	Absolute		
Relapse												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	5/12 (41.7%)	5/13 (38.5%)	RR 1.08 (0.41 to 2.83)	31 more per 1000 (from 227 fewer to 704 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL
Adverse events												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	2/12 (16.7%)	0/13 (0%)	OR <sup>4</sup> 8.79 (0.52 to 149.55)	170 more per 1000 (from 70 fewer to 400 more) <sup>3</sup>	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Limited baseline characteristics. Open study. Randomised at induction.

<sup>2</sup> Crosses both the lower (0.75) and upper (1.25) relative risk (RR) MIDs.

<sup>3</sup> Risk difference has been calculated

<sup>4</sup> Peto odds ratio.

**Table 113: Azathioprine versus azathioprine and olsalazine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine	Azathioprine & Olsalazine	Relative (95% CI)	Absolute		
Relapse - 1 year												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/34 (8.8%)	4/36 (11.1%)	RR 0.79 (0.19 to 3.29)	23 fewer per 1000 (from 90 fewer to 254 more)	⊕○○○ VERY LOW	CRITICAL
Relapse - 2 years												
1	randomised	very	no serious	no serious	very	none	5/34	6/36	RR 0.88 (0.3	20 fewer per 1000	⊕○○○	CRITICAL

	trials	serious <sup>1</sup>	inconsistency	indirectness	serious <sup>2</sup>		(14.7%)	(16.7%)	to 2.63	(from 117 fewer to 272 more)	VERY LOW	
<b>Quality of life - IBDQ (Better indicated by higher values)</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	34	36	-	MD 0 higher (17.13 lower to 17.13 higher)	⊕○○○ VERY LOW	CRITICAL
<b>Serious adverse events</b>												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/34 (8.8%)	3/36 (8.3%)	RR 1.06 (0.23 to 4.89)	5 more per 1000 (from 64 fewer to 324 more)	⊕○○○ VERY LOW	IMPORTANT

<sup>1</sup> Overall unclear method of randomisation and allocation concealment. Single blind.

<sup>2</sup> Crosses both the lower (0.75) and upper (1.25) relative risk (RR) MIDs.

#### Additional information which could not be meta-analysed:

**Adverse events:** It was unclear in the MANTZARIS2004<sup>134</sup> study whether the adverse events reported were the number of events or the number of patients experiencing one or more event. However, it is noted that there were significant differences in the number of transient leukopenia events (5 in the azathioprine group and 12 in the azathioprine and olsalazine group).

**Table 114: Methotrexate versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Placebo	Relative (95% CI)	Absolute		
Relapse at 9 months												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	9/14 (64.3%)	8/18 (44.4%)	RR 1.45 (0.76 to 2.76)	200 more per 1000 (from 107 fewer to 782 more)	⊕⊕○○ LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> >10% difference in missing data between the treatment arms. Randomised at induction.

<sup>2</sup> Crosses the upper (1.25) relative risk (RR) MID.

#### Additional data that could not be meta-analysed:

**Adverse events:** OREN1996<sup>160</sup> study only reported the adverse events that resulted in withdrawal from the study. These were transient leukopenia (n=1) and migraine (n=1) in the methotrexate group and a severe rash (n=1) in the placebo group.

**Table 115: Methotrexate versus 5-ASA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	5-ASA	Relative (95% CI)	Absolute		
Relapse - 24 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	5/7 (71.4%)	2/2 (100%)	RR 0.82 (0.41 to 1.64)	180 fewer per 1000 (from 590 fewer to 640 more)	⊕○○○ VERY LOW	CRITICAL
Relapse - 56 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	6/7 (85.7%)	2/2 (100%)	RR 0.97 (0.53 to 1.79)	30 fewer per 1000 (from 470 fewer to 790 more)	⊕○○○ VERY LOW	CRITICAL
Relapse - 76 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	6/7 (85.7%)	2/2 (100%)	RR 0.97 (0.53 to 1.79)	30 fewer per 1000 (from 470 fewer to 790 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup>Unclear method of randomisation, allocation concealment and blinding. >10% difference in missing data between the treatment groups. Randomised at induction.

<sup>2</sup>Crosses both the lower (0.75) and upper (1.25) relative risk (RR) MIDs.

**Table 116: Mercaptopurine versus methotrexate**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6-Mercaptopurine	Methotrexate	Relative (95% CI)	Absolute		
Relapse - 24 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	2/11 (18.2%)	5/7 (71.4%)	RR 0.25 (0.07 to 0.97)	536 fewer per 1000 (from 21 fewer to 664 fewer)	⊕○○○ VERY LOW	CRITICAL
Relapse - 56 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	3/11 (27.3%)	6/7 (85.7%)	RR 0.32 (0.12 to 0.87)	583 fewer per 1000 (from 111 fewer to 754 fewer)	⊕○○○ VERY LOW	CRITICAL
Relapse - 76 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	4/11 (36.4%)	6/7 (85.7%)	RR 0.42 (0.18 to 0.98)	497 fewer per 1000 (from 17 fewer to 703 fewer)	⊕○○○ VERY LOW	CRITICAL

Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Unclear method of randomisation, allocation concealment and blinding. Randomised at induction.

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

**Table 117: Mercaptopurine versus 5-ASA**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6-Mercaptopurine	5-ASA	Relative (95% CI)	Absolute		
Relapse - 24 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	2/11 (18.2%)	2/2 (100%)	RR 0.25 (0.07 to 0.84)	750 fewer per 1000 (from 160 fewer to 930 fewer)	⊕○○○ VERY LOW	CRITICAL
Relapse - 56 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	3/11 (27.3%)	2/2 (100%)	RR 0.35 (0.13 to 0.97)	650 fewer per 1000 (from 30 fewer to 870 fewer)	⊕○○○ VERY LOW	CRITICAL
Relapse - 76 weeks												
1	randomised trials	very serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	4/11 (36.4%)	2/2 (100%)	RR 0.45 (0.19 to 1.09)	550 fewer per 1000 (from 810 fewer to 90 more)	⊕○○○ VERY LOW	CRITICAL
Quality of life												
0	no evidence available					none	-	-	-	-		CRITICAL

<sup>1</sup> Unclear method of randomisation, allocation concealment and blinding. >10% difference in missing data between the treatment arms. Randomised at induction.

<sup>2</sup> Crosses the lower (0.75) relative risk (RR) MID.

## 7.23 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix K to aid consideration of cost-effectiveness.

In addition to drug costs, costs would be incurred in the due to monitoring blood levels to ensure therapeutic response. The costs of monitoring are provided in Table 118 below.

**Table 118: Costs of monitoring**

Type of test	Unit cost	Source
Full blood count	£3	NHS reference costs <sup>55</sup> (code DAP823)
Renal function test	£1	NHS reference costs <sup>55</sup> (code DAP841)
Liver function test	£1	NHS reference costs <sup>55</sup>
TPMT assay	£26	Crohn's guideline <sup>148</sup>

## 7.24 Evidence statements

### 7.24.1 Clinical evidence statements

#### 7.24.1.1 Azathioprine versus placebo

##### Relapse

Azathioprine may be clinically more effective at reducing relapse rates, irrespective of whether the patients were randomised with active disease or in remission or in combination with steroids or sulphasalazine [low and very low quality evidence, 1 study, N=67, 1 study, N=35, 2 studies, N=120]

##### Adverse events

There may be no clinical difference in adverse event rates between azathioprine and placebo [very low quality evidence, 2 studies, N=130]

#### 7.24.1.2 Azathioprine versus sulphasalazine

##### Relapse

There may be no clinical difference in the reduction of relapse rates between azathioprine and sulphasalazine in combination with steroids at 18 months [very low quality evidence, 1 study, N=25]

##### Adverse events

Sulphasalazine may have a lower adverse event rate compared to azathioprine [very low quality evidence, 1 study, N=25]

### 7.24.1.3 Azathioprine versus azathioprine & olsalazine

#### Relapse

There may be no clinical difference in the reduction of relapse rates between azathioprine and azathioprine & olsalazine at 1 and 2 years [very low quality evidence, 1 study, N=70]

#### Quality of life

There may be no clinical difference in quality of life between azathioprine and azathioprine & olsalazine [very low quality evidence, 1 study, N=70]

#### Serious adverse events

There may be no clinical difference in serious adverse event rates between azathioprine and azathioprine & olsalazine [very low quality evidence, 1 study, N=70]

### 7.24.1.4 Methotrexate versus placebo

#### Relapse

Placebo may be clinically more effective at reducing relapse rates compared to methotrexate at 9 months [Low quality evidence 1 study, N=32]

### 7.24.1.5 Methotrexate versus 5-ASA

#### Relapse

Methotrexate may be clinically more effective at reducing relapse rates compared to 5-ASA at 24 weeks, but there may be no clinical difference at 56 and 76 weeks [very low quality evidence, 1 study, N=9]

### 7.24.1.6 Mercaptopurine versus methotrexate

#### Relapse

Mercaptopurine may be clinically more effective at reducing relapse rates compared to methotrexate at 24, 56 and 76 weeks [very low quality evidence 1 study, N=18]

### 7.24.1.7 Mercaptopurine versus 5-ASA

#### Relapse

Mercaptopurine may be clinically more effective at reducing relapse rates compared to 5-ASA at 24, 56 and 76 weeks [very low quality evidence 1 study, N=13]

## 7.24.2 Economic evidence statements

No relevant economic evaluations were identified.

## 7.25 Recommendations and link to evidence

<b>Recommendations</b>	<b>Maintaining remission in people with ulcerative colitis</b>
	<b>Proctitis and proctosigmoiditis</b>  <b>27.To maintain remission after a mild to moderate inflammatory</b>



	<p>exacerbation of proctitis or proctosigmoiditis, consider the following options, taking into account the person's preferences:</p> <ul style="list-style-type: none"> <li>• a topical aminosalicylate<sup>z</sup> alone (daily or intermittent) or</li> <li>• an oral aminosalicylate<sup>aa</sup> plus a topical aminosalicylate<sup>z</sup> (daily or intermittent) or</li> <li>• an oral aminosalicylate<sup>aa</sup> alone, explaining that this may not be as effective as combined treatment or an intermittent topical aminosalicylate alone.</li> </ul> <p><b>Left-sided and extensive ulcerative colitis</b></p> <p><b>28.To maintain remission in adults after a mild to moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• offer a low maintenance dose of an oral aminosalicylate</li> <li>• when deciding which oral aminosalicylate to use, take into account the person's preferences, side effects and cost.</li> </ul> <p><b>29.To maintain remission in children and young people after a mild to moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• offer an oral aminosalicylate<sup>mm</sup></li> <li>• when deciding which oral aminosalicylate to use, take into account the person's preferences (and those of their parents or carers as appropriate), side effects and cost.</li> </ul> <p><b>All extents of disease</b></p> <p><b>30.Consider oral azathioprine<sup>nn</sup> or oral mercaptopurine<sup>nn</sup> to maintain remission:</b></p> <ul style="list-style-type: none"> <li>• after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids or</li> <li>• if remission is not maintained by aminosalicylates.</li> </ul> <p><b>31.To maintain remission after a single episode of acute severe ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• consider oral azathioprine<sup>nn</sup> or oral mercaptopurine<sup>nn</sup></li> <li>• consider oral aminosalicylates in people who cannot tolerate or who decline azathioprine and/or mercaptopurine, or in whom azathioprine and/or mercaptopurine are contraindicated.</li> </ul>
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<sup>mm</sup> At the time of publication (June 2013), 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. Dosing requirements for children should be calculated by body weight, as described in the BNF.

<sup>nn</sup> Although use is common in UK clinical practice, at the time of publication (June 2013) azathioprine and mercaptopurine did not have a UK marketing authorisation for this indication. 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.

	<p><b>Dosing regimen for oral aminosalicylates</b></p> <p><b>32. Consider a once-daily dosing regimen for oral aminosalicylates<sup>oo</sup> when used for maintaining remission. Take into account the person's preferences, and explain that once-daily dosing can be more effective, but may result in more side effects.</b></p>
Relative values of different outcomes	<p>The GDG considered the following outcomes direct measures that indicated long term maintenance of remission:</p> <ul style="list-style-type: none"> <li>• Relapse (author defined)</li> <li>• Health related quality of life (any validated indexes).</li> </ul> <p>These were considered the critical outcomes in making decisions about the maintenance of remission.</p> <p>The GDG considered the following outcomes should also be considered when making decisions on appropriate treatments for the maintenance of remission:</p> <ul style="list-style-type: none"> <li>• Adverse events</li> <li>• Serious adverse events</li> <li>• Colectomy</li> <li>• Hospitalisations.</li> </ul>
Trade off between clinical benefits and harms	<p>The GDG recommended different treatment options for proctitis/proctosigmoiditis and left sided/extensive ulcerative colitis based on clinical experience. Topical preparations are thought not to extend to the colon and are unsuitable for treating people with left sided or extensive disease.</p> <p><b>Proctitis/proctosigmoiditis</b></p> <p>The evidence for recommendation 27 is limited and is reflected in the strength of the recommendation. The evidence demonstrated benefit for both topical ASAs and topical budesonide<sup>127</sup> in maintaining remission compared to placebo. Based on clinical experience and the safety concerns of using long term corticosteroids the GDG made a recommendation for the use of topical ASAs. Very low quality evidence found a higher dose of a topical ASA (1g suppositories) may be more beneficial than a lower dose (500mg).<sup>12,47</sup> The GDG considered the absence of evidence in this area comparing topical preparations or doses and were unable to make a recommendation on preparation or dose.</p> <p><b>Mode of application</b></p> <p>Intermittent topical ASAs were found to be clinically more effective in reducing relapse rates compared to oral ASAs [low quality evidence, 2 studies, N=69]. Intermittent topical treatment in the trials is defined as the first seven days of the month (D'Albaso<sup>48</sup>), twice weekly (Andreoli<sup>3</sup>) and every third night (Mantzaris<sup>133</sup>). The GDG recognised however that some people would prefer to use an oral ASA rather than a topical treatment and included this as a treatment option for people with proctitis or proctosigmoiditis. The recommendation makes it clear that this may not be as effective a treatment option but that it may be better than no treatment.</p> <p>In relation to combination treatment (oral plus topical treatment) the evidence was limited. Continuous oral ASAs and intermittent topical ASAs were found</p>

<sup>oo</sup> At the time of publication (June 2013), not all oral aminosalicylates had a UK marketing authorisation for once-daily dosing. 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.

to be clinically more effective in reducing relapse rates compared to oral ASAs alone [moderate quality evidence, 2 studies, N=96].<sup>46,231</sup> The GDG recognised there may be benefit for combination therapy and added this to the recommendation 27 as a 'consider'.

### **Children**

Recommendation 27 includes children and young people. None of the studies included children or young people and the adult evidence was extrapolated. The GDG noted that topical treatments are rarely used in children in the UK. Support and education could improve compliance to the use of topical steroids and ASAs in children and young people.

### **Left sided/ extensive ulcerative colitis**

#### **Mesalazine/ASA preparations**

As noted in the introduction the BNF states that: The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable. In order to address this, mesalazines were compared to each other where possible and disease extent was explored where heterogeneity was present. The mesalazines were also compared to the other ASAs where possible. The direct evidence was limited and mostly of low to very quality and did not demonstrate that any one mesalazine or ASA preparation was clinically more effective than another.

The oral mesalazines listed in the BNF are Asacol, Ipocol, Mesren, Mezavant, Octasa, Pentasa and Salofalk. The reviews in this guideline name the mesalazine as it is named in the studies. We are aware that the mesalazines can change brand names, for example Mesren was been rebranded as Octasa 400 in December 2012.

Recommendation 28 is supported by evidence from network meta-analyses (NMA) and these data were used in the health economic model.

The NMAs showed that all the treatments were better than placebo, it should be noted all the confidence intervals overlapped. Due to the limitations of the NMA (almost all comparisons were based on single studies, a few of which were small studies with large confidence intervals; very low or low quality studies; SASP tolerant populations in trials; varying times in remission prior to enrolling in trial; the extent of disease often not recorded/ precise with a risk of indirect populations; and the use of different indexes for remission) there is insufficient evidence to be confident of one treatment's superiority compared to another for the maintenance of remission. In addition, other mesalazines are available (Mesren, Octasa) but none of the studies named these mesalazines and so the GDG were unable to comment on their efficacy.

There were not any clinically significant differences between the low dose oral ASAs and this was the same for the high dose oral ASAs. A dose effect was not observed between lower and higher doses of ASAs but in the clinical review a dose relationship was suggested and in an NMA that compared combined high doses and combined low dose, the high dose ASAs were more effective than low dose ASAs or placebo.

In the first NMA, the probability of the treatment having fewer withdrawals due to adverse event was highest in oral mesalazine and beclometasone (72.8%) and balsalazide (13.0%).

The health economic showed that it was cost-effective to maintain patients on a low dose ASA. The costs of ASA had an impact on the results as all strategies

became more cost-effective if cheaper brands were used.

After evaluating the evidence, clinical and patient representative experience and considering the limitations from the NMA and health economic model the GDG were confident to offer a low maintenance dose of an oral ASA.

#### **Combination therapy**

There was some evidence to support the use of oral ASA and intermittent ASA enemas but the GDG recognised there would be issues around acceptability and tolerability and this was not thought a treatment option widely chosen in practice. However the GDG were keen to offer this as a treatment option when an oral ASA alone is not working or to avoid an immunomodulator and recognised that it was about patient choice.

#### **Children and young people**

Recommendation 29 is specific to children and young people. None of the studies included children or young people; whilst the adult evidence was extrapolated according to the treatments, the GDG could not recommend a 'low' dose ASA and recognised that paediatric doses should be calculated by body weight, as described in the children's BNF.

#### **Regimen**

Very low to low quality evidence showed there is no clinical difference between taking a once a day dose of an oral ASA compared to conventional dosing (more than once a day) although the side effects may be greater with once daily dosing.<sup>62,115</sup> The GDG recognised that some people would prefer a once daily dosing regimen but acknowledged the evidence was limited and that the benefit needs to outweigh the risk of possible additional adverse and serious adverse events. This is reflected in recommendation 32. The GDG noted that if people did experience side effects with once daily dosing the dose should be split across the day.

#### **Immunomodulators**

The evidence on the use of immunomodulators was limited and after taking into account the adverse events associated with immunomodulators compared to ASAs the GDG felt that none of the immunomodulators should be recommended first line in place of ASAs. However the GDG recognised that in the following circumstances treatment options are limited: after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids; after a single episode of acute severe ulcerative colitis; or if remission is not maintained by ASAs. It is important for this population to have access to this treatment option despite the absence of evidence and this has been reflected in recommendation 30.

The GDG acknowledged that the use of immunomodulators indicated a need for monitoring and reflected this in recommendation 18.

#### **Acute severe ulcerative colitis**

The GDG discussed the population of people who had experienced an episode of acute severe ulcerative colitis but were unable to tolerate or who decline azathioprine or mercaptopurine. The treatment options for this population are limited and the GDG noted the absence of evidence. The GDG thought it was important there was a treatment option for this group and made a weak recommendation for oral ASAs to be considered in this situation.

Economic considerations	<p><b>Proctitis/ proctosigmoiditis</b></p> <p>No cost-effectiveness evidence was identified. The costs of topical ASA and steroids are dependent on the formulation and the daily dose administered. However, it is possible that cost savings could be made if a suppository is used over an enema and if intermittent dosing is chosen over daily dosing. If an oral ASA is added to or chosen over a topical ASA, initial treatment costs would increase. This was supported by two studies<sup>46,164</sup> which showed that there are increased drug costs associated with combination therapy; however combination treatment may be better for maintaining remission. There were a number of limitations with the studies as outlined in the economic evidence profile. Briefly, the studies were based on a non-UK health setting, the methodology was unclear and results were presented as costs per relapse avoided which made interpretation difficult. It is plausible however, that if patients are successfully maintained in remission, downstream costs due to additional drug use and hospitalisations could be reduced. In addition, benefits to the patient would include improvement of symptoms and quality of life. The GDG therefore considered that costs of maintenance with drugs would be offset by these potential benefits.</p> <p><b>Left-sided and extensive</b></p> <p>A systematic literature search identified two studies evaluating the costs effectiveness of drugs for the maintenance of remission in this subgroup. A US study by Yen<sup>230</sup> showed that compared to no maintenance, 2.4g/day maintenance treatment had an incremental cost-effectiveness ratio of £146,000/QALY. The results were influenced by the estimates of ASA efficacy used, ASA costs, as well as resource use specific to the US. The GDG noted that there were issues surrounding the applicability of this study as some health state utilities were inferred from a Crohn's disease and the model was based on a non-UK population. A study by Connolly<sup>40</sup> addressed the use of two ASA maintenance dosing regimens: once daily versus twice daily. Once daily dosing was found to be cost-effective.</p> <p>The studies addressed issues that the GDG considered relevant when considering treatment options for maintenance of remission. However, not all the clinical evidence addressed in the clinical review section was used in these studies. In addition, the GDG considered that clarification on the use of a high or low maintenance dose of ASA after a flare of disease would be useful. Because of the uncertainty in this area, the GDG considered it a high priority for economic analysis.</p> <p>Based on this, a decision-analytic model was developed which addressed the use of no maintenance, a low maintenance dose or high maintenance dose of an oral ASA for the maintenance of remission.</p> <p>The model showed that it was cost-effective to maintain patients on a low dose ASA. The costs of ASA had an impact on the results as all strategies became more cost-effective if cheaper brands were used.</p> <p>In interpreting the results, limitations of the model as highlighted below needed to be considered:</p> <ul style="list-style-type: none"> <li>• The costs and dis-utilities of drug-specific adverse events were not captured in the model due to lack of robust data. This means that the cost-effectiveness of all the treatments strategies has been over-estimated although the magnitude is unknown as each drug is likely to have a different, specific side-effect profile. This introduces uncertainty around interpretation of the results.</li> <li>• It was assumed in the model that all relapses have the same severity. The GDG noted that patients could experience a flare requiring escalation to therapy not captured in the model. This means that the</li> </ul>
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	<p>cost-effectiveness for the comparators may have been over estimated.</p> <ul style="list-style-type: none"> <li>• Mesalazines, such as Mesren and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment about the relative efficacy of these mesalazines hence caution should be exercised when generalising the results of this model.</li> <li>• Patients who withdraw from treatment were assumed to still be in remission. This is a conservative approach. If withdrawal from treatment results in flare of disease, the cost-effectiveness of all comparators may have been overestimated in the model.</li> <li>• Treatment adherence was assumed to be 100% in the model. The GDG however noted that this may not be the case in reality and measures to improve adherence are discussed elsewhere in the guideline.</li> </ul> <p><b>Immunomodulators</b></p> <p>The GDG considered the costs of the immunomodulators and the associated monitoring in people with acute severe ulcerative colitis or those who have two or more flares in 12 months requiring systemic steroids. These costs were thought to be justified as benefits and cost saving would be incurred due to reduction in the adverse events associated with repeated flares and avoidance of systemic steroid use.</p>
Quality of evidence	<p>The majority of the evidence for the outcomes was of low to very low quality and consisted of some mixed populations. There were a limited number of studies. There was no evidence for oral steroids.</p> <p>The NMA was based on a total of 18 studies of 11 different interventions, all of which were mono-therapies. The majority of the evidence for the outcomes had a rating of low to very low quality. For more detail see the limitations listed above for the NMA and health economic model.</p> <p>The GDG noted that evidence about the following oral ASAs was identified: sulphasalazine, balsalazide, olsalazine and mesalazine. The brand names of the mesalazines in the published papers were Asacol and Pentasa. Mezavant XL, Ipocol, Mesren and Octasa were not named in the papers.</p> <p>There were very few studies looking at the use of immunomodulators, the evidence for the outcomes were all very low quality.</p> <p>The impact of extent of disease was difficult to evaluate as the majority of the studies evaluating oral treatments had mixed extent populations and the studies evaluating topical treatments had in the majority proctitis/proctosigmoiditis populations.</p>
Other considerations	<p>The GDG has listed the low maintenance doses of all the aminosalicylates. The GDG defined low maintenance doses as: 1.5g Salofalk; 2g Pentasa; 1.2g all Asacol, Octasa, Mezavant XL, Ipocol; 1g Olsalazine; 3g Balsalazide and 2g sulfasalazine. The GDG definition was based on the ranges of doses in the drugs' summary of product characteristics and the dose comparisons used in the clinical evidence reviews.</p> <p>The GDG are aware that the mesalazines can be called different brand names in different countries (for example, Mesren is marketed as Asacol in Japan) and can be rebranded in the same country (for example Mesren has now been rebranded as Octasa 400 in the UK). This further complicates the issue that the mesalazine preparations are stated as 'may not be interchangeable' in the BNF and in then identifying a preferred mesalazine.</p> <p>From GDG experience some patients might prefer intermittent ASA</p>

suppositories for distal disease. The GDG patient representatives felt that patient preference might tend towards suppositories as opposed to enemas for the topical preparations as it is easier to control the dose.

The GDG felt that once daily dosing of oral ASA may improve adherence but this decision should be made by the patient (and/or their parents or carers as appropriate) taking into account the associated costs and likelihood of their adherence.

Recommendation 30 considers the use of azathioprine or mercaptopurine. The GDG note that azathioprine is metabolised to mercaptopurine.

Mercaptopurine may be tolerated in some patients who have not tolerated azathioprine for example, in those with headaches or flu like symptoms. However, the GDG felt that mercaptopurine should not be used in patients who have had pancreatitis or hepatotoxicity whilst on azathioprine.

The GDG acknowledged the issues around the length of time people should stay on maintenance therapy. The clinical evidence was for 6-24 months and the health economic analysis used a time horizon of 24 months. There may be a protective effect against colorectal cancer with long term use of ASAs and so the GDG felt unable to make an additional recommendation or comment on how long people should stay on maintenance therapy. The GDG recognised the importance of screening for colorectal cancer in people with ulcerative colitis.

In addition, the GDG debated at length whether there may be some situations in which maintenance treatment is not required, or may not be cost-effective. They felt that there was insufficient information on prognostic features, which might identify sub-groups of such individuals, to make such a recommendation.

#### **Research recommendation**

The GDG agreed that the lack of evidence on maintaining remission in people with ulcerative colitis justified developing a research recommendation. For further information on the research recommendations see Appendix M.

## 8 Pregnant women

### 8.1 Clinical introduction

With the peak occurrence of ulcerative colitis in women of child-bearing age, women and clinicians are often faced with issues relating to planning a pregnancy and the management of ulcerative colitis during a pregnancy. Such issues can create difficult dilemmas for the pregnant woman and clinicians.

Women may seek advice about the effects of ulcerative colitis on pregnancy and the effect of the pregnancy on ulcerative colitis. Information relating to the safety of medication during pregnancy for ulcerative colitis is a central part of such discussions. This can then be set against possible benefits from optimal control of disease activity.

The critically important measures of outcome were considered to be maternal mortality, the occurrence of intrauterine fetal loss (stillbirth or spontaneous miscarriage), premature births, children with low birth weight and the occurrence of congenital abnormalities. In interpreting the available evidence, it was recognised that randomized controlled trials were very unlikely to be available in pregnant women. In addition, the occurrence of adverse outcomes – for example congenital abnormalities – may be rare, and studies may not be of sufficient size to demonstrate a difference from the background rate of occurrence for these outcomes.

A review question and protocol was therefore designed to address the outcome of pregnancy associated with the medications considered for use in induction and maintenance of remission. Many drugs used to treat ulcerative colitis are unlicensed. Drugs should be used if their potential benefit outweighed their risk with the exception of methotrexate. Methotrexate is known to be teratogenic with the BNF advising that effective contraception is required during and for at least three months after treatment in men or women<sup>105</sup>, and was therefore excluded from further consideration in this section. Sulphasalazine may be associated with folate deficiency and attention should be paid to appropriate folate supplementation if the drug is used. 5-aminosalicylic acid, corticosteroids and azathioprine / mercaptopurine cross the placenta.<sup>16,20,37,54</sup> Concern has been raised about the possible association of corticosteroids with a greater than expected occurrence of fetal cleft palate – in humans and rodents – though there remains uncertainty about this effect.<sup>69</sup> Azathioprine / mercaptopurine has been reported to be associated with congenital abnormalities in animal studies and with poorer outcomes in transplant recipients<sup>8</sup> and in combined registries<sup>38,156</sup> – though it has remained difficult to determine the effect of the underlying conditions or other confounding factors (which may not be ulcerative colitis) in these studies.

On the basis of meta-analysis, a normal pregnancy is expected in 85% of women with ulcerative colitis.<sup>143</sup> There is always a risk of miscarriage and of birth abnormalities in all pregnancies regardless of a diagnosis of UC. There has also been a consensus that disease activity during pregnancy, including early in the pregnancy, affects outcomes.<sup>10,228</sup> The review protocol was therefore designed to try to capture evidence regarding disease activity and outcome.

Much of the literature considers ulcerative colitis and Crohn's disease together as an inflammatory bowel disease (IBD) cohort. For this evidence review, it was felt that there were sufficient important differences between ulcerative colitis and Crohn's disease to only consider evidence relating to ulcerative colitis.



## 8.2 Review question: What are the consequences of using drug treatments for the induction and maintenance of remission in pregnant women?

For full details see review protocol in Appendix C.

The treatment options that are available to people with ulcerative colitis for the induction and maintenance of remission have previously been reviewed. However, for these review questions only randomised controlled trials were included. No papers were identified that included pregnant women with ulcerative colitis (active or in remission). A further search has been carried out including other study designs to determine whether any of the drugs used for the treatment of ulcerative colitis are not appropriate for use during pregnancy.

There were no restrictions for study duration. The data in the studies has been reported as narrative summaries.

## 8.3 Clinical evidence

Eleven studies were included in the review.<sup>17,22,24,81,124,131,153,155,174,202,210</sup> Evidence from these are summarised in the clinical evidence profiles below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix G and exclusion list in Appendix F.

The studies looked at aminosalicylates (sulphasalazine, mesalazine, olsalazine, and unspecified 5-ASA), corticosteroids (prednisolone, hydrocortisone, unspecified enemas) and immunomodulators (azathioprine, mercaptopurine, ciclosporin and infliximab) for the induction and maintenance of remission during pregnancy and their effect on birth outcomes. There were no studies looking at tacrolimus and balsalazide.

The following factors were considered to be important confounders:

- Age
- Smoking status
- Alcohol
- Ethnicity
- BMI
- Socioeconomic status
- Parity
- Gestational age
- Severity of disease
- Co-morbidities
- Concomitant medication
- Nutritional status

Only two studies<sup>81,210</sup> reported data for those who experienced active and inactive disease whilst taking 5-aminosalicylates during pregnancy. Three studies<sup>24,124,174</sup> reported results for patients with active severe or hospitalised relapse of ulcerative colitis using a combination of treatments during pregnancy. The remaining studies' data were unable to be separated.

### Secondary evidence

There were no systematic reviews identified that looked specifically at pregnant women with ulcerative colitis and the effect of medical treatments on birth outcomes. Two systematic

reviews<sup>42,94</sup> were identified for inflammatory bowel disease but they contained no separate analysis for ulcerative colitis populations and were excluded.

### Primary evidence

None of the 11 studies reported any data on quality of life. Two studies<sup>124,174</sup> reported no maternal mortality.

#### BELL1997<sup>17</sup>

A prospective case series study looked at the pregnancy outcome of 16 women with distal ulcerative colitis who were dependent on topical 5-ASA to prevent relapses. The women were on either 4g 5-ASA enemas three times a week or 500mg 5-ASA suppository nightly from conception to delivery apart from two women who stopped treatment, consequently relapsed and then went back onto the same topical therapy 12 weeks later.

The only drug reported was 5-ASA (topical) (N= 19 pregnancies, 16 women). All 19 pregnancies were normal full term births. There were no congenital abnormalities reported or growth and development problems during follow up (2months-5 years, median 2 years).

#### BORTOLI2011<sup>22</sup>

A prospective cohort study looked at the pregnancy outcome of inflammatory bowel disease patients. 187 ulcerative colitis pregnant women and 187 controls (pregnant non IBD women) were included. The data were collected by electronic case report forms, personal or telephone interviews and review of the patient's medical records. No doses or duration of medical treatments were reported.

5-ASA monotherapy (mesalazine) (N=88): thirty-seven women were on high dose 5-ASA ( $\geq 3\text{g/day}$ ) at conception, most of which maintained the same dose during the pregnancy. Ninety-five per cent of the mothers had a normal live birth. There were four premature deliveries, one spontaneous abortion, one therapeutic abortion and no reported congenital abnormalities. Overall the mesalazine therapy group did not demonstrate any statistical significance for live birth, spontaneous abortion, therapeutic abortion, or differences in birth weight. There was a statistically significant lower premature birth rate (multivariate logistic regression), for those on 5-ASA monotherapy and increased risk of preterm delivery if on combination treatment.

Immunomodulator therapy (azathioprine, ciclosporin, corticosteroids, infliximab) (N=14): There were no statistically significant differences found for live birth, spontaneous abortion, therapeutic abortion, preterm delivery and birth weight (multivariate logistic regression). No congenital abnormalities were reported.

Combination of 5-ASA and immunomodulators therapy (N=63): There were no statistically significant differences found for live birth, spontaneous abortion, therapeutic abortion and birth weight (multivariate logistic regression). Premature delivery was greater with the use of the combination therapy ( $p=0.004$ ). No congenital abnormalities were reported.

Non IBD pregnant controls (N=187): There were 170 live births (167 classed as normal births), 15 spontaneous abortions, 14 premature deliveries and 3 congenital abnormalities.

#### BRANCHE2009<sup>24</sup>

##### Active disease

A retrospective case series study looked at the effect of ciclosporin in the treatment of steroid refractory severe ulcerative colitis during pregnancy on birth outcomes. Data were collected from medical records and through contact with the patient's general practitioners. All patients received

oral and IV steroids (median duration of 14 days and 7 days respectively). The majority of patients received 2mg/kg/day of ciclosporin (one patient received 4mg/kg/day) for a median of 7 days (range 5-17). Seven patients improved. The one patient that did not improve was later found to have Crohn's disease. Two patients also had azathioprine in addition to oral ciclosporin. Oral ciclosporin was continued for a median 107 days (range 7-253). Four patients were on steroids at the time of delivery.

The drugs reported were ciclosporin and steroids (N=8 (2 patients also received azathioprine)). Seven women had normal births and one had a spontaneous abortion at 22 weeks gestation (in utero death). This woman had received 90 days of ciclosporin and the spontaneous abortion was thought to be related to maternal S-protein deficiency. The patient went on to have a successful pregnancy a year later. There were four premature births and one low birth weights (32 weeks). There were no congenital abnormalities, renal side effects or severe infections noted in the first months of life (median follow up time 38 months, range 12-79 months)

#### HABAL1993<sup>81</sup>

A prospective case series study looked at pregnant women with ulcerative colitis or Crohn's disease who were dependent on 5-ASA due to risk of relapse when stopping treatment. There were 10 women (12 pregnancies) with ulcerative colitis all of whom were in remission at conception. There were 6 weekly obstetric reviews or earlier if there was a relapse. The dose of mesalazine (Asacol) continued at the same level as prior to pregnancy (mean 1.7g/day, range 0.8-2.4g). Other medications (steroids (oral/enema) or 5-ASA enema) may be added in the event of a relapse.

The drugs reported were mesalazine (oral +/- enema) (N=8) and mesalazine and steroid (oral +/- enema) (N=4): Of the women that received mesalazine (oral +/- enema) (N=8) three patients experienced a relapse, two of which had 5-ASA enemas in addition to oral mesalazine. Six women continued oral mesalazine until term, and one stopped at 12 weeks gestation and went on to have a colectomy. Seven were delivered at term and one pregnancy had a spontaneous abortion. There were no congenital, clinical or biochemical abnormalities, low birth weights, abnormal growth or development or low Apgar scores (<6).

Of the women that received mesalazine and steroid (oral +/- enema) (N=4) one patient experienced a relapse, whilst the other three women remained in remission. Two patients took 10mg a day of prednisolone, one took 5mg a day of prednisolone and one had hydrocortisone enemas in addition to oral mesalazine. All the babies were delivered at term. There were no congenital, clinical or biochemical abnormalities, low birth weights, abnormal growth or development or low Apgar scores (<6).

#### LEVY1981<sup>124</sup>

##### Active disease

A retrospective case series study looked at 31 pregnant women (60 pregnancies) with a diagnosis of ulcerative colitis from five hospitals in Israel during 1970-1979. The case records were reviewed and the patients were also interviewed. Out of these patients 11 women were hospitalized for the deterioration of ulcerative colitis and the treatment and birth outcomes were reported for 8 of them. There was no information on dose and duration of therapy, only those reported were on the drugs for at least two weeks. The remaining women who were in remission did not receive any treatment.

The drugs reported were sulphasalazine (N=1), sulphasalazine and steroids (oral/topical) (N=5), sulphasalazine and azathioprine (N=1), sulphasalazine, azathioprine and prednisolone (N=1): All the women received sulphasalazine until delivery (unknown dose). Steroid treatment was given to two women for more than two months, and for about five months in the other three women. It was reported by the author that "no special problems arose and no fetal abnormalities were found". There were no maternal mortalities reported.

LUDVIGSSON2002<sup>131</sup>

A cross-sectional study which was part of the All Babies In Southeast Sweden (ABIS) study which was a prospective screening programme for the prediction of autoimmune diseases. One questionnaire was completed shortly after birth and a second at home, to confirm their IBD diagnosis. When the diagnosis was unclear, an attempt would be made to contact the woman by telephone and interviewed. In the event that the diagnosis was still unclear, the woman's regular doctor would be contacted. Twins were excluded. Autoimmune controls were also recruited. The only data that could be extracted that would look at the relationship of birth outcomes to the medication used during pregnancy was for birth weight. Dose and duration of treatment was not described.

The drugs reported were mesalazine (N=5), mesalazine and steroids (N=4), steroids (N=3), sulphasalazine (N=2), mesalazine and sulphasalazine (N=1), olsalazine (N=1) and no 5-ASA/steroid treatment (N=10). Only one of the 26 births had a baby with a low birth weight (<2.5kg) the mother was taking mesalazine and steroids. There was no information on premature birth which could be a main confounder in these results. Overall there were two premature births but it is unclear if one of these was the mother who had the neonate with a low birth weight.

NIELSON1983<sup>153</sup>

The retrospective cohort study followed 97 women (173 included pregnancies) over a 12 year period. The medical records of the women were examined, and where there was insufficient information the women were contacted by telephone or letter. There was no information on dose and limited information on duration of treatment.

The author concluded that there were no more babies with jaundice born to mothers on sulphasalazine, and that the use of corticosteroids did not increase the frequency of spontaneous abortions, premature births or congenital abnormalities.

The drugs reported were sulphasalazine (N=46), systemic/topical corticosteroids (N=17) and sulphasalazine & systemic/topical corticosteroids (N=23). For the women receiving sulphasalazine (N=46) there were 31 normal births, 1 congenital abnormality<sup>pp</sup>, 8 spontaneous abortions and one premature birth. For the women receiving systemic/topical corticosteroids (N=17): there were 16 normal births and 1 spontaneous abortion. For the women receiving sulphasalazine & systemic/topical corticosteroids (N=23): there were 21 normal births (one twin), 4 of which were premature and 1 spontaneous abortion.

Eighty-eight women received no treatment, there were 68 normal births, 4 of which were premature, 2 congenital abnormalities and 6 spontaneous abortions.

NORGARD2003A<sup>155</sup>

This retrospective cohort study included women who had a live birth or a still birth after the 28<sup>th</sup> week of gestation. The data were collected through a population registry, pharmacy data through the National Health Service, birth registry and County hospital data. If there was any uncertainty about the data, the hospital records were retrieved. The only reported data on the relationship between medication use for ulcerative colitis and birth outcomes was on the use of 5-ASA drugs throughout pregnancy. There was no information on the doses used.

The only drug reported was 5-ASA (N=65). There were 3 low birth weight babies, 7 premature births (2 induced and 4 spontaneous), 3 stillbirths (2 unknown causes at 28.6 and 33.6 weeks, possible strangulation of the umbilical cord at 43 weeks) and in those exposed in the period from 30 days

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<sup>pp</sup> It is unclear which congenital abnormality the child had. Overall there were three children that had the following abnormalities reported: Left sided luxatio coxae, persistent ductus arteriosus, coarctation of the aorta, left sided coronary hypoplasia and bilateral renal aplasia, aplasia of the external genitalia, aplasia of the urinary bladder, bilateral club foot plus polydactyly of the right hand.

prior to conception to the end of the first trimester (N=42) there were 3 congenital abnormalities (unclear if one baby had aphakia or atresia of the lacrimal duct, 2 were not reported clearly, risk of misclassification bias).

Logistic regression was used to analyse the data, which adjusted for the mother's age (below 25 years, 25-29 years, and 30 years or more), parity (1 or >1) and smoking (yes/no). Low birth weight and stillbirths were also adjusted for gestational age (32 weeks or less, 33-36 weeks, and 37 weeks or more).

The use of 5-ASA suggested an increase in premature births (OR 2.4, 95% CI 1.1-5.3) and still births (OR 8.4, 95% CI 2.0-34.3).

#### REEDY2008<sup>174</sup>

##### Active disease

This retrospective case control study enrolled women with inflammatory bowel disease who suffered a severe relapse and were hospitalised during pregnancy (N=11 ulcerative colitis). The controls were age- matched pregnant women (IBD matched) that did not require hospitalization for their inflammatory bowel disease (N=25 ulcerative colitis). Other major medical conditions were excluded from the control group. There were no maternal mortalities reported.

All women were given hydrocortisone. Other drugs that were taken in combination were: sulphasalazine, ciclosporin, mercaptopurine, 5-ASA (oral/enema) and cortenema (corticosteroid enema).

Two women who were given hydrocortisone (oral/IV) needed a colectomy, one later went on to deliver a low birth weight premature baby (1.7kg, 36 weeks) and no information was available for the other woman. There were three other women in which information on the birth outcomes were unable to be retrieved.

One woman had a spontaneous abortion at 15 weeks, who had taken hydrocortisone and ciclosporin and consequently went in to remission.

Four out of the five other pregnancies were all low birth weights (1-1.2kg), and four were premature (26-35 weeks). Three women had taken either sulphasalazine or 5-ASA with corticosteroids, and two women had taken ciclosporin.

#### SIDDIQUE2011<sup>202</sup>

A prospective cohort study followed 60 women with ulcerative colitis over a two year period. Thirty of these women were pregnant. Twenty four of the pregnant women suffered a mild exacerbation of ulcerative colitis which was controlled by increasing the dose of mesalazine. Four had a moderate disease exacerbation and were treated with oral steroids and two had a severe attack necessitating the use of IV steroids followed by oral steroids in the first trimester. All of the women were reported to have delivered normally at the time of birth, with no reported growth retardation or congenital abnormalities.

#### TRALLORI1994<sup>210</sup>

A prospective cohort study followed 16 pregnant women (19 pregnancies) who were in remission and taking oral/topical or a combination of 5-ASA treatment. The women were seen regularly at an outpatient clinic and their assessments recorded. The doses used were 1.2g of mesalazine (Asacol) a day orally and 4g 5-ASA enema twice a week. Women who relapsed were treated with 20mg of corticosteroids IM per day for 1 month and 1.6g 5-ASA a day orally which dropped to 1.2g after their symptoms had improved.

The drugs reported were 5-ASA (N=15) and 5-ASA and steroids (N=4). Of the women that received 5-ASA (N=15) all 15 women remained in remission, 13 of which had normal births. There was one induced abortion and one spontaneous abortion (2<sup>nd</sup> trimester). Of the women that received 5-ASA and steroids (N=4) four women who relapsed and required steroids to induce remission. Three of these had normal births and one had an induced abortion.

### **Quality assessment**

The quality of this evidence was very low, many of the studies were retrospective cohort studies or case control studies with mixed inflammatory bowel populations. The lack of comparison groups, baseline characteristics and methodological adjustments that occurred in most of the studies meant there is a high risk of confounders influencing the results. Disease severity is a main confounder as it is closely linked to the use of medical therapies in ulcerative colitis.

Most of the studies did not describe the doses and duration of treatment of the drugs and it is difficult to determine patient compliance. It could be assumed that those on long term maintenance therapy may be more adherent to treatment but without any prior knowledge of the patient's education level and knowledge of the disease it is not possible to make this assumption.

The majority of the studies and their outcomes are very low quality due to their study design and additional limitations identified in the review process. Most of the studies were downgraded for limited or no baseline characteristics and lack of adjustment for confounding variables. The only study which is of a low quality is the BORTOLI2011 paper, a prospective cohort study which adequately controlled for the main confounders.

## **8.4 Economic evidence**

### **Published literature**

No relevant economic evaluations were identified.

### **New cost-effectiveness analysis**

New analysis was not prioritised for this area.

## **8.5 Evidence summary**

### **8.5.1 Clinical summary**

Eleven studies were included in the clinical review on the use of drug treatments for ulcerative colitis during pregnancy. There was limited information available due to the paucity of evidence specifically for the ulcerative colitis population. Many studies were excluded due to them having a mixed population and not controlling for diagnosis. The studies that were included were of low to very low quality and did not control for confounding variables apart from one study<sup>22</sup>. Therefore, there is insufficient good quality evidence to determine whether particular drugs used for the induction or maintenance of ulcerative colitis during pregnancy have any adverse effects on the pregnancy that outweigh their clinical benefits.

### **8.5.2 Economic summary**

No relevant economic evaluations were identified.

## 8.6 Recommendations and link to evidence

Recommendations	<p><b>Pregnant women</b></p> <p><b>33. When caring for a pregnant woman with ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• <b>Ensure effective communication and information-sharing across specialties (for example, primary care, obstetrics and gynaecology, and gastroenterology).</b></li> <li>• <b>Give her information about the potential risks and benefits of medical treatment to induce or maintain remission and of no treatment, and discuss this with her. Include information relevant to a potential admission for an acute severe inflammatory exacerbation.</b></li> </ul>
Relative values of different outcomes	<p>None of the literature searches completed for the review questions within the guideline excluded pregnancy as a condition. However, the drug intervention comparison studies identified in the reviews on induction and maintenance of remission did in fact exclude pregnant women from the studies. In order to identify any evidence on the use of drug treatments in pregnant women with ulcerative colitis an additional review with different study designs was done.</p> <p>The outcomes in the induction and maintenance reviews were relevant as well as those identified below. The outcomes considered most important to the decision making were stillbirth, congenital abnormalities, spontaneous abortion, premature births (&lt;37 weeks gestation), low birth weight (&lt;2.5kg) and maternal mortality. Other outcomes considered were normal birth (live birth with no abnormalities) and quality of life.</p>
Trade off between clinical benefits and harms	<p>The GDG considered the benefits and risks associated with potential relapses and maintenance therapy during pregnancy for both the woman and her foetus.</p> <p>Eleven studies were included in the review. The studies looked at aminosalicylates (sulphasalazine, mesalazine, olsalazine, and unspecified 5-ASA), corticosteroids (prednisolone, hydrocortisone, unspecified enemas) and immunomodulators (azathioprine, mercaptopurine, ciclosporin and infliximab) for the induction and maintenance of remission during pregnancy and their effect on birth outcomes. There were no studies on tacrolimus, beclometasone dipropionate and balsalazide.</p> <p>Only two studies<sup>81,210</sup> reported data for those who experienced active and inactive disease whilst taking 5-aminosalicylates during pregnancy. Three studies<sup>24,124,174</sup> reported results for patients with active severe or hospitalized relapse of ulcerative colitis using a combination of treatments during pregnancy. It was not possible to separate data from the remaining studies.</p> <p>There is no clear evidence of harm from any specific treatment although it was difficult to be certain based on the poor study design (case series that did not control for confounders), small sample sizes and because the use of drug treatments were not the primary aim of the studies. Due to these limitations, the GDG noted the evidence should be interpreted with caution.</p> <p>There is an absence of evidence of any different clinical effects of the treatments during pregnancy because the studies did not measure these outcomes.</p> <p>None of evidence sufficiently demonstrated that disease activity contributed</p>

	<p>to adverse outcomes (no statistical analysis was carried out in the studies). However, the GDG felt that it was likely that disease activity could contribute to adverse outcomes.</p> <p>5-ASA may protect against premature birth (reduced frequency of premature birth), but when used in combination with immunomodulators, there was an associated higher rate of premature birth. The study controlled for disease activity.<sup>22</sup></p> <p>After reviewing the evidence the GDG felt unable to make a recommendation on the potential harms or benefits of specific drug treatments in pregnant women with ulcerative colitis.</p>
Economic considerations	<p>The provision of information may require additional clinic visits but the GDG considered the potential costs of this to be offset by the benefits.</p>
Quality of evidence	<p>The majority of the evidence identified was of very low quality. This was primarily due to the following limitations:</p> <ul style="list-style-type: none"> <li>• The studies have mostly a prospective or retrospective cohort design.</li> <li>• The study design meant that a causal relationship could not be determined.</li> <li>• There were no or limited baseline characteristics documented or adjustments made for confounders.</li> <li>• Most of the studies had an overall inflammatory bowel disease population. The evidence in some of the review has been extracted from the overall population.</li> <li>• The majority of the studies do not report the dose or duration of treatment given.</li> <li>• It was difficult to determine patient compliance.</li> <li>• In all of the studies the blinding of investigators was unclear.</li> <li>• No studies reported azathioprine alone in participants with ulcerative colitis.</li> <li>• No evidence about longer term maternal wellbeing, quality of life or disease activity after delivery.</li> </ul>
Other considerations	<p>The GDG recognised the importance of treating active disease. Therefore the recommendations made are based on GDG consensus.</p> <p>The GDG thought it was important to recommend the collaboration of multiple specialities involved in the care of the pregnant woman.</p> <p>Due to the uncertainty of the effect of drug treatments on birth outcomes, the GDG felt it necessary to emphasize the importance of informing the women about all her treatment options including the possibility of a severe inflammatory exacerbation of ulcerative colitis.</p> <p>The GDG noted the absence of evidence in pregnant women with ulcerative colitis and recognised this was a difficult area within which to conduct studies. The GDG proposed a registry of pregnant women with ulcerative colitis would be beneficial to provide information on drug treatments.</p> <p><b>Research recommendation</b></p> <p>The GDG agreed that the lack of evidence on induction and maintenance of remission in pregnant women with ulcerative colitis justified developing a research recommendation. For further information on the research recommendations see Appendix M.</p>



## 9 Monitoring

### 9.1 Clinical introduction: monitoring bone health

Evaluation of bone health is considered an important aspect of chronic disease management in inflammatory bowel disease (IBD), particularly in children and young people who are considered a vulnerable group. The problems with bone health (osteopenia/osteoporosis) as assessed by bone mineral density (BMD) are thought to be less severe in ulcerative colitis than Crohn's disease; severe osteopenia is identified in 3-6% compared to 12-18% of children and young people respectively.

The most objective measure of bone health is that of BMD, currently best measured by dual-energy x-ray absorptiometry (DEXA); abnormality defined as Z score  $\leq -2$  SD below mean. However there are recognised limitations to use of DEXA in children and young people including around the relationship between abnormalities in BMD and fracture risk.

The factors influencing bone health are multifactorial. The reason children and young people are considered more vulnerable is due to rapid physiological periods of skeletal growth, pubertal development and process of bone mineralisation for which appropriate nutrient (including, minerals and vitamins e.g. calcium, vitamin D) and hormonal (growth hormone, sex steroid) factors need to be met. Furthermore, the process of bone mineralisation leading to attainment of peak bone mass can occur any time from late childhood to early adulthood (up to mid-20s) and is the key determinant of life-long skeletal health including subsequent adult fracture risk due to osteopenia/osteoporosis.

During the active disease state in IBD, clinicians need to consider how bone development and health may be disturbed due to a number of factors including; increased circulating pro-inflammatory cytokines, poor nutrition, corticosteroid treatment, decreased physical mobility, delayed puberty and in girls, primary or secondary amenorrhea. In addition, consideration should be given to other co-existing conditions or risk factors which may pre-dispose to osteopenia/osteoporosis and or vitamin D deficiency. The clinical relevance of different levels of vitamin deficiency is debatable and not fully supported by evidence but the subject of consensus opinion<sup>qq</sup>.

The aim of clinicians is to identify those at risk of poor bone health to enable the most time-effective intervention to optimally support both the physiological and disease activity related demands on maintaining skeletal health during the potential vulnerable period before peak bone mass is achieved. In addition to predisposing risk factors, other biochemical and radiological methods of testing may be useful in diagnosis and or monitoring of bone health.

### 9.2 Review question: In children and young people with ulcerative colitis, are disease activity, systemic corticosteroid use, total vitamin D and malnutrition, risk factors for poor bone health?

For full details see review protocol in Appendix C.

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<sup>qq</sup> Recent expert consensus statements and reviews have made recommendations about treatment goals for Vitamin D in patient groups considered to be at risk. Serum concentrations of 25, hydroxy, Vitamin D [25(OH)D] are agreed to be the most robust marker for overall vitamin D status: levels of  $>75\text{nmol/L}$  are optimal;  $<75 - 50$ , suboptimal and  $<50\text{nmol/L}$  deficient associated with disease risk.

### 9.3 Clinical evidence: monitoring bone health in children and young people

Five studies were included in the review.<sup>21,60,162,194,195</sup> Evidence from this is summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, study evidence table in Appendix G and exclusion list in Appendix F.

In all of the studies it was unclear which variables had been inputted into the multivariate analysis. There were no studies that met our inclusion criteria that looked at malnutrition. Many of the included studies looked at BMI or weight but not specifically a reduction of 2 centiles in weight.

Bone mineral density was the only dependent variable out of our outcomes that was reported in the studies. One study reported no fractures.<sup>21</sup> None of the other outcomes (epiphyseal fusion, bone age) were reported in the multivariate analyses as a dependent variable (outcome). The incidence of osteoporosis or osteopenia was reported in one study<sup>60</sup>.

The majority of studies that looked at the predefined risk factors were excluded due to the following reasons:

- Mixed ulcerative colitis and Crohn's population with only uni-variate analysis or multivariate analysis without controlling for diagnosis.
- Uni-variate analysis only; therefore does not control for confounding variables.
- Mixed adult and child population without separate results.

## 9.4 Evidence profile

### 9.4.1 Bone health

Table 119: Bone health

Study characteristics			Quality assessment						
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings	Quality
BOOT1998	Retrospective and prospective study Cross-sectional and longitudinal data. Netherlands, unclear setting.	N=36 UC patients out of N=55 in the total population.	Very serious <sup>1</sup>	N/A	No ne	N/A		Diagnosis (Crohn's / UC), cumulative dose of prednisolone and BMI SAS as determinants and BMD SDS as the dependent variable. Cumulative dose of prednisolone and diagnosis related significantly to lumbar spine BMD SDS and explained 20% of the variance  Only diagnosis related significantly to total body BMD SDS in the regression mode (r <sup>2</sup> =15%)	LOW

Study characteristics			Quality assessment						
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Summary of findings	Quality
ELHODHOD2012	Prospective case control study, Egypt, Paediatric Gastroenterology Unit	N=27 UC patients out of N=47 in the total population	Very serious <sup>2</sup>	N/A	None	N/A		<p>Multivariate analysis did not find 1, 25 (OH)<sub>2</sub> D<sub>3</sub> a significant predictor of BMD when patients experience a flare of disease (treated with oral steroids and antibiotics followed by maintenance 5ASA).</p> <p><b>Frequency of osteopenia and osteoporosis in flare and remission:</b></p> <p>UC flare: normal BMD n=3 (11.1%), mild degree n=0, severe degree n=24 (88.9%)</p> <p>UC remission: normal BMD n=11 (40.7%), mild degree n=6 (22.2%), severe degree n=10 (37%)</p>	LOW
PAGANELLI2007	Retrospective and prospective study. Cross-sectional data.	N=21 UC patients out of N=56 in the total population	Very serious <sup>3</sup>	N/A	None	N/A		<p>None of the risk factors (disease activity, cumulative corticosteroid use, vitamin D (25OHD)) were identified as predictors of low BMD in the multivariate analysis. It is unclear exactly which variables were included in this analysis</p>	LOW
SCHMIDT2009/2011	<p>Cross-sectional study and 2 year follow up study</p> <p>Sweden, two paediatric hospitals</p>	N=83 UC patients out of N=144 IBD patients studied	Very serious <sup>4</sup>	N/A	None	N/A	Outcome of corticosteroid use was not cumulative	<p>Neither treatment with prednisolone, disease category, nor disease duration turned out to represent risk factors for lower BMD in this model at baseline. At 2 years follow up disease subcategory and treatment with azathioprine or corticosteroids were not significantly associated with a lower change in BMD.</p>	VERY LOW

<sup>1</sup> Cross-sectional data, unclear whether the population is representative (unclear enrolment to the trial), unclear whether there was missing data, unclear how the lifetime cumulative corticosteroid dose was calculated and very limited information reported for the multivariate analysis.

<sup>2</sup> Unclear whether the population is representative (enrolment to the trial), unclear whether there was missing data, unclear and very limited description of the multivariate analysis. Inadequate covariates/events ratio

<sup>3</sup> Mainly cross-sectional data, limited information reported for the multivariate analysis, missing data is not described, and some important confounders were not considered

<sup>4</sup> Cross-sectional study followed by a prospective cohort, unclear how the patients were recruited( consecutive/ random), no dose/ duration of corticosteroid use, limited information reported for the multivariate analysis, missing data is not described, and some important confounders were not considered.

## 9.5 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Vitamin D testing: estimated at £13 per test<sup>rr</sup>

DEXA scan: estimated at £72 per scan<sup>ss</sup>

## 9.6 Evidence statements

### 9.6.1 Clinical evidence statements

None of the studies assessed the relationship between disease activity, systemic corticosteroid use, total vitamin D, malnutrition and the incidence of fractures or osteoporosis /osteopenia.

No relationship was identified between corticosteroid use (3 studies, very low to low quality evidence), total vitamin D (2 studies, low quality evidence) disease activity (1 study, low quality evidence) and total body BMD score. One study (low quality evidence) found cumulative dose of prednisolone and diagnosis related significantly to lumbar spine BMD SDS. None of the studies assessed the relationship between malnutrition and total BMD score.

### 9.6.2 Economic evidence statements

No relevant economic studies were identified.

## 9.7 Recommendations and link to evidence

Recommendations	
	<b>Monitoring bone health</b>
	<b>Adults</b>
	<b>34. For recommendations on assessing the risk of fragility fracture in adults, refer to Osteoporosis: assessing the risk of fragility fracture (NICE clinical guideline 146).</b>
	<b>Children and young people</b>

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<sup>rr</sup> NHS Derby City and NHS Derbyshire county 2011  
([http://www.derbyshiremedicinesmanagement.nhs.uk/images/content/files/Prescribing%20Guidelines/Vitamin%20D%20Position%20Statement%20\(with%20test%20cost%20change\).pdf](http://www.derbyshiremedicinesmanagement.nhs.uk/images/content/files/Prescribing%20Guidelines/Vitamin%20D%20Position%20Statement%20(with%20test%20cost%20change).pdf))

<sup>ss</sup> NHS reference costs 2010-2011 (Diagnostic imaging outpatient RA15Z)

	<p><b>35. Consider monitoring bone health in children and young people with ulcerative colitis in the following circumstances:</b></p> <ul style="list-style-type: none"> <li>• during chronic active disease</li> <li>• after treatment with systemic corticosteroids</li> <li>• after recurrent active disease.</li> </ul>
Relative values of different outcomes	<p><b>Children and young people</b></p> <p>The critical outcomes were the incidence of fractures (validated by medical records/radiological reports), osteoporosis/osteopenia as indicated by bone mineral density Z-score and reduction in bone mineral density score.</p> <p>The important outcomes were epiphyseal fusion (normal, delayed) and bone age (wrist x-ray, delayed, normal or advanced).</p> <p>The potential risk factors considered where:</p> <ul style="list-style-type: none"> <li>• Disease activity (active versus inactive disease)</li> <li>• Systemic corticosteroid use: current high dose use versus current low dose use, frequent use (&gt;2 times/year) versus infrequent use (≤2 times/year), cumulative dose</li> <li>• Total vitamin D (25-hydroxycholecalciferol)</li> <li>• Malnutrition (reduction by 2 centiles in weight)</li> </ul> <p>Bone mineral density (BMD) was the only dependent variable out of our outcomes that was reported in the studies. One study reported no fractures. None of the other outcomes (epiphyseal fusion, bone age) were reported in the multivariate analyses as a dependent variable (outcome). The incidence of osteoporosis or osteopenia was not included as a dependant variable.</p>
Trade off between clinical benefits and harms	<p>The identification of risk factors that contribute to poor bone health is important to indicate when to monitor, and then to adjust treatment if necessary, to reduce the risk of fractures and further deterioration of bone health. The GDG were not aware of any harms in monitoring bone health. The review did not evaluate the different methods of assessing bone health and their relative benefits and harms, and as such no one method for monitoring is recommended.</p> <p>The GDG noted that there was a lack of evidence demonstrating an increase in fracture risk in the studies identified, and were unable to suggest that osteoporosis, with the implied increased risk of fracture, is a common feature of the disease. The GDG also found that it was unclear whether the studies which presented DEXA scan data fully adjusted for body size rather than age. The GDG considered that in any chronic disease, growth is impaired. The GDG acknowledged that DEXA scanning does not fully adjust for bone size and underestimates BMD in small bones, so there is a risk that both osteopenia and osteoporosis are over-diagnosed in children with chronic disease.</p> <p>The GDG also noted that undertaking DEXA imaging after every episode of active disease or in less than 6 monthly intervals would be considered too frequent. Not only would it be unlikely there would be sufficient change over this period the risks of radiation exposure should be considered.</p> <p>The evidence from the review did not demonstrate that any of the risk factors contributed to poor bone health.</p>
Economic considerations	<p>The GDG considered that as monitoring would not be carried out routinely, the cost of monitoring is likely to be offset by long term benefits. Benefits include reducing the risk of fractures and preventing further deterioration of bone health. In addition, downstream cost savings could be made if the use of drugs</p>

	to treat poor bone health is avoided.
Quality of evidence	<p>There were four studies, three were rated as low quality and one as very low quality. One study found cumulative dose of prednisolone and diagnosis related significantly to lumbar spine BMD standard deviation scores. No other evidence identified these or any of the other potential risk factors as predictors for poor bone health.</p> <p>The GDG were concerned about the poor quality of the evidence and the noted the following limitations of the studies:</p> <ul style="list-style-type: none"> <li>• The studies were poorly designed with small sample sizes.</li> <li>• It was unclear how representative the studies were of a UK paediatric ulcerative colitis population.</li> <li>• It was unclear about the levels of missing data.</li> <li>• Important confounders were not always included in multivariate analysis.</li> <li>• It was unclear in two studies that measured corticosteroid use how it was being measured (i.e. how the lifetime cumulative corticosteroid dose was calculated).</li> </ul> <p>For these reasons the GDG were not confident in concluding from the evidence whether disease activity, cumulative corticosteroid dose, total vitamin D and malnutrition are risk factors for poor bone health.</p>
Other considerations	<p>As a result of the absence of good quality evidence the recommendation was based on GDG consensus with expert advisor input and this is reflected in the strength of the recommendation.</p> <p>There is a need for further research in this area. Experience from the GDG indicated two of the risk factors identified above (active disease and systemic corticosteroid use) could result in poor bone health and considered it appropriate to consider monitoring when these risk factors are present.</p> <p>The rationale for considering these risk factors was that during active disease the production of interleukin 6 may affect bone formation. Steroids are commonly associated with lowering bone density and increasing the incidence of fractures. Both these factors are identified as risk factors for monitoring bone health in adults in the NICE clinical guideline on Osteoporosis: assessing the risk of fragility fracture (NICE clinical guideline 146).</p> <p>The GDG has less experience and confidence in making a recommendation concerning vitamin D and malnutrition.</p> <p>The GDG agreed that decisions should be considered based on the clinical picture. The GDG did not wish to specify the method of monitoring.</p>

## 9.8 Clinical introduction: monitoring growth and pubertal development in children and young people

Assessment of growth, including measurement of both weight and height and staging of puberty are generally considered a very important aspect of clinical assessment in children and young people with chronic disease including chronic inflammatory bowel disease (IBD). In ulcerative colitis under-nutrition and, in particular, growth failure (short stature) and or pubertal delay are thought to occur less commonly than in Crohn's disease, however, nutritional deficiencies can develop quickly during periods of active disease.<sup>182</sup> At the time of new IBD diagnosis, low body mass index (BMI) was seen in ~ 8% of ulcerative colitis.<sup>191</sup> However, short stature and pubertal delay is thought to occur to a far



lesser extent and it is anticipated that most children with ulcerative colitis will reach their expected adult height<sup>136,219</sup> and achieve normal milestones of pubertal development.

Clinicians must take into account potential reasons for growth failure and pubertal delay. These may be due to intrinsic factors related to disease, such as, disease severity including extent, complications, duration of symptoms prior to achieving disease control and frequency of disease relapse or extrinsic factors, such as duration and frequency of steroid use. Consideration should also be given to identify other co-existing conditions that may predispose to growth failure and pubertal delay such as eating disorders or other causes of primary growth hormone and gonadotropin deficiency secondary to poor nutritional status.

The clinician needs to consider the most appropriate assessments in children and young people to identify those at risk of faltering growth and pubertal delay and the optimal frequency of monitoring needed. In clinical practice, weight and height recording (including parental heights with mid-parental height estimation), documentation on age and sex appropriate growth chart and Tanner pubertal staging undertaken by trained healthcare professionals are considered important assessments for growth and puberty respectively. Consideration should be given to alternative methods for assessing puberty, including self-assessment, to take into account the sensibilities of children and young people to allow for discreet assessment and to aid compliance. Additional supplementary assessments to investigate or monitor when poor growth is suspected may include use of wrist x-ray to measure bone age in pre-pubertal children and predict remaining growth potential or biochemical markers including IGF1 (insulin-like growth factor 1), as the biological mediator of growth hormone action.

The necessary frequency of assessments will depend on the degree to which growth and puberty are impaired at disease presentation and subsequent disease course and severity. Specific parameters to assess might include:

- growth failure (fall off across two centile lines in weight or height on growth chart)
- and/or pubertal delay
- and/or lack of age- and gender-appropriate progression of puberty once it has started (Tanner stage).

Prompt recognition of cause for growth failure and or pubertal delay is necessary to allow for timely intervention; this is particularly important when active disease including associated steroid use may coincide with the potential vulnerable periods of rapid skeletal growth during pubertal development. The aim of timely intervention is to maximise adult height potential and complete pubertal development.

## **9.9 Review question: In children and young people with ulcerative colitis, what are the optimal strategies (timing, location) for monitoring growth?**

The purpose of this review is to determine whether the monitoring of children and young people's growth and pubertal development should be carried out at specific time points in relation to the activity of their ulcerative colitis and use of corticosteroids. The use of self-monitoring compared to medical monitoring will also be considered, and whether there needs to be special measures taken over the transitional period.

There were no limitations on the settings for the studies, and no trial duration or sample size restrictions.

## 9.10 Clinical evidence: monitoring growth and pubertal development

No studies were identified that met the inclusion criteria for either review.

See the study selection flow chart in Appendix E and exclusion list in Appendix F.

Studies were identified that looked at the use of corticosteroids but not in relation to how frequent the monitoring should take place. They only demonstrated that the use of corticosteroids depending on the dose and duration of treatment could affect growth in children and young people.

Some studies commented on the fact that growth should be monitored within their conclusions, but the frequency in which it should be carried out was not evidenced. There were also some guidelines and clinical recommendations<sup>77,96</sup> found in the search but they were consensus and lacked a referenced clinical evidence base.

## 9.11 Economic evidence

### Published literature

No relevant economic evaluations were identified.

### New cost-effectiveness analysis

New analysis was not prioritised for this area.

## 9.12 Evidence statements

### 9.12.1 Clinical evidence statements

No relevant clinical papers were identified.

### 9.12.2 Economic evidence statements

No relevant economic evaluations were identified.

## 9.13 Recommendations and link to evidence

<p><b>Recommendations</b></p>	<p><b>Monitoring growth and pubertal development in children and young people</b></p> <p><b>36. Monitor the height and body weight of children and young people with ulcerative colitis against expected values on centile charts (and/or z scores) at the following intervals according to disease activity:</b></p> <ul style="list-style-type: none"> <li>every 3–6 months: <ul style="list-style-type: none"> <li>– if they have an inflammatory exacerbation and are approaching or undergoing puberty or</li> <li>– if there is chronic active disease or</li> <li>– if they are being treated with systemic corticosteroids</li> </ul> </li> <li>every 6 months during pubertal growth if the disease is inactive</li> <li>every 12 months if none of the criteria above are met.</li> </ul>
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	<p><b>37. Monitor pubertal development in young people with ulcerative colitis using the principles of Tanner staging, by asking screening questions and/or carrying out a formal examination.</b></p> <p><b>38. Consider referral to a secondary care paediatrician for pubertal assessment and investigation of the underlying cause if a young person with ulcerative colitis:</b></p> <ul style="list-style-type: none"> <li>• has slow pubertal progress or</li> <li>• has not developed pubertal features appropriate for their age.</li> </ul> <p><b>39. Monitoring of growth and pubertal development:</b></p> <ul style="list-style-type: none"> <li>• can be done in a range of locations (for example, at routine appointments, acute admissions or urgent appointments in primary care, community services or secondary care)</li> <li>• should be carried out by appropriately trained healthcare professionals as part of the overall clinical assessment (including disease activity) to help inform the need for timely investigation, referral and/or interventions, particularly during pubertal growth.</li> </ul> <p><b>If the young person prefers self-assessment for monitoring pubertal development, this should be facilitated where possible and they should be instructed on how to do this.</b></p> <p><b>40. Ensure that relevant information about monitoring of growth and pubertal development and about disease activity is shared across services (for example, community, primary, secondary and specialist services). Apply the principles in Patient experience in adult NHS services (NICE clinical guideline 138) in relation to continuity of care.</b></p>
Relative values of different outcomes	<p><b>Growth</b></p> <p>The critical outcomes were deviation from normal/baseline height (growth velocity) as measured on the centile chart trajectory and bone age (wrist x-rays) in pre-pubertal children. The important outcome was deviation from normal weight as measured by the weight centiles.</p> <p><b>Pubertal development</b></p> <p>The critical outcomes were delayed puberty (as indicated by assessment on the Tanner staging) and quality of life.</p>
Trade off between clinical benefits and harms	<p>Growth and pubertal delay are important markers of wellbeing in children and young people with ulcerative colitis. Poor growth may be an indicator of poor disease control and delayed growth and puberty can result in feelings of isolation from peers. Early detection of any delay will allow treatment to be adjusted according to the patient's need and avoid further growth retardation and promote catch up growth.</p> <p>The benefits of measuring growth and pubertal development are clear but the frequency of measurement is not. There could be a risk that monitoring growth too frequently could pick up 'false delay in growth' and treatment could be changed unnecessarily resulting in changes to treatment that are premature.</p>

Economic considerations	<p>The GDG considered that the monitoring of growth and pubertal development in children and young people should already be routinely carried out in clinical practice. If the frequency of monitoring recommended by the GDG is above what is currently offered, it may require patients to make additional appointments. Costs would be incurred due to additional resource use, for example, staff time. However, if monitoring occurs when patients make their routine clinic visits, costs may not be substantially higher than in usual care. If costs are increased, however, the GDG thought that the benefits for the child's development would outweigh these costs.</p>
Quality of evidence	<p>No studies were identified that indicated any optimal timing strategies for monitoring growth or pubertal development.</p>
Other considerations	<p>The recommendations are based on GDG consensus.</p> <p><b>The need for monitoring</b></p> <p>The GDG noted the need to be aware of the potential for growth and pubertal delay in children and young people with ulcerative colitis, particularly at high risk times. High risk times, from clinical experience, are defined as during disease relapse, persistent disease, approaching puberty and when taking corticosteroids. Restricted growth in children and young people can indicate poor disease control.</p> <p>In the GDG's experience, children and young people with restricted growth or pubertal delay can feel embarrassed and different from their peers, which can impact on their social and emotional development. Suspected delay should be addressed swiftly and appropriate referrals made.</p> <p><b>Growth measurement</b></p> <p>The GDG recognised the difficulties of accurately and reliably measuring growth in children and young people, and the consequences of measuring growth too frequently. They discussed extensively the optimal frequency of monitoring.</p> <p>The GDG noted that growth is typically measured by mapping linear growth and weight onto centile charts, and considered this to be the most appropriate method of measuring growth in children and young people with ulcerative colitis. The GDG recognised the problems in obtaining reliable height and weight measurements, and noted the importance of appropriately trained staff and calibrated equipment (stadiometers) for accurate height measurement.</p> <p>The recording of Z-scores is considered to be more accurate as they represent all values which sit between the centile lines. However, healthcare professionals are less familiar with this technique; therefore the GDG recommended that Z-scores should be recorded where possible. Radiologic determination of bone age by wrist x-ray compared to chronological age can help inform discussion with children and young people about their remaining growth potential.</p> <p>The GDG discussed the risks of unreliable measurement if linear growth is measured too frequently (less than 6 monthly). However, the GDG considered the benefits of monitoring growth regularly outweighed any potential risks of infrequent sporadic monitoring, and that, in the context of a child or a young person with concerns about growth, too large an interval to try to establish an accurate diagnosis of growth failure might delay timely treatment intervention. In the absence of evidence, the GDG considered disease activity to be a reasonable marker for defining frequency. The more severe the disease activity and use of systemic corticosteroids, the greater the potential for growth delay.</p>

### **Pubertal measurement**

The GDG noted there are varying definitions of when delayed puberty starts, with estimates of around 14 years. The recommendation states ‘has not developed pubertal features appropriate for their age’ to allow clinicians to make judgements according to the young person and to allow appropriate investigation and monitoring of growth and puberty. This enables treatment to be started early (if needed) with better outcomes.

In the absence of any evidence about the optimal strategies for monitoring pubertal development, the GDG agreed that the Tanner staging was a widely recognised tool for measuring pubertal stages, and was appropriate for use in children and young people with ulcerative colitis.

Monitoring pubertal development is a sensitive topic, and the GDG agreed that monitoring should only be done by professionals with an expertise in paediatrics. Local protocols should be available. Self-assessment can be an alternative for children and young people. This option should be considered and support offered to children and young people that take up this option.

### **Growth and pubertal development**

The recommendations have been ordered to reflect the need to undertake the monitoring assessments at the same time. They are all part of the overall clinical assessment, including disease activity, to help inform the need for timely investigation.

The GDG recognised that there could be more than one setting where children and young people could have their growth monitored (for example, GP, school nurse, consultant or specialist nurse), and the importance of communicating information across services.

### **Research recommendation**

The GDG agreed that the lack of evidence on delayed growth and pubertal development in children and young people with ulcerative colitis justified developing research recommendations. For further information on the research recommendations see Appendix M.

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## 11 Acronyms and abbreviations

<b>5-ASA</b>	5-aminosalicylate
<b>ACA</b>	Available case analysis
<b>AE</b>	Adverse events
<b>ASA</b>	Aminosaliclylate
<b>BD</b>	Bis in die (twice a day)
<b>CAI</b>	Clinical activity index
<b>DAI</b>	Disease activity index
<b>HR</b>	Hazard ratio
<b>IGA</b>	Investigator's global assessment
<b>ITT</b>	Intention to treat analysis
<b>LOCF</b>	Last observation carried forward
<b>OD</b>	Omne in die (once a day)
<b>PFA</b>	Patient's functional assessment
<b>PGA</b>	Physician's global assessment
<b>PPA</b>	Per protocol analysis
<b>RCT</b>	Randomised controlled trial
<b>SAE</b>	Serious adverse event
<b>SASP</b>	Sulphasalazine
<b>Steroids</b>	Corticosteroids
<b>TDS</b>	Ter die sumendum (three times a day)
<b>UCDAI</b>	Ulcerative colitis disease activity index

## 12 Glossary

<b>Abstract</b>	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
<b>Algorithm (in guidelines)</b>	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
<b>Allocation concealment</b>	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
<b>Applicability</b>	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
<b>Arm (of a clinical study)</b>	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
<b>Association</b>	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
<b>Baseline</b>	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
<b>Beclometasone dipropionate</b>	A type of corticosteroid. Also known as ‘beclomethasone dipropionate’.
<b>Before-and-after study</b>	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
<b>Bias</b>	Systematic (as opposed to random) deviation of the results of a study from the ‘true’ results that is caused by the way the study is designed or conducted.
<b>Blinding</b>	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
<b>Carer (caregiver)</b>	Someone other than a health professional who is involved in caring for a person with a medical condition.
<b>Case-control study</b>	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
<b>Case-series</b>	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
<b>Clinical efficacy</b>	The extent to which an intervention is active when studied under controlled research conditions.



<b>Clinical effectiveness</b>	The extent to which an intervention produces an overall health benefit in routine clinical practice.
<b>Clinician</b>	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
<b>Cochrane Review</b>	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
<b>Cohort study</b>	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
<b>Comorbidity</b>	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
<b>Comparability</b>	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
<b>Concordance</b>	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
<b>Confidence interval (CI)</b>	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
<b>Confounding</b>	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
<b>Consensus methods</b>	Techniques that aim to reach an agreement on a particular issue. Consensus methods may be used when there is a lack of strong evidence on a particular topic.
<b>Control group</b>	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
<b>Cost benefit analysis</b>	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

<b>Cost-consequences analysis (CCA)</b>	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
<b>Cost-effectiveness analysis (CEA)</b>	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
<b>Cost-effectiveness model</b>	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
<b>Cost-utility analysis (CUA)</b>	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
<b>Credible Interval</b>	The Bayesian equivalent of a confidence interval.
<b>Decision analysis</b>	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
<b>Discounting</b>	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
<b>Dominance</b>	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
<b>Drop-out</b>	A participant who withdraws from a trial before the end.
<b>Economic evaluation</b>	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
<b>Effect (as in effect measure, treatment effect, estimate of effect, effect size)</b>	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
<b>Effectiveness</b>	See 'Clinical effectiveness'.
<b>Efficacy</b>	See 'Clinical efficacy'.
<b>Epidemiological study</b>	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
<b>EQ-5D (EuroQol-5D)</b>	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
<b>Evidence</b>	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials,

	observational studies, expert opinion (of clinical professionals and/or patients).
<b>Exclusion criteria (literature review)</b>	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
<b>Exclusion criteria (clinical study)</b>	Criteria that define who is not eligible to participate in a clinical study.
<b>Extended dominance</b>	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
<b>Extrapolation</b>	In data analysis, predicting the value of a parameter outside the range of observed values.
<b>Follow-up</b>	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
<b>Generalisability</b>	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
<b>Gold standard See 'Reference standard'.</b>	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
<b>Harms</b>	Adverse effects of an intervention.
<b>Health economics</b>	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
<b>Health-related quality of life (HRQoL)</b>	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
<b>Heterogeneity Or lack of homogeneity.</b>	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
<b>Imprecision</b>	Results are imprecise when studies include relatively few patients and

	few events and thus have wide confidence intervals around the estimate of effect.
<b>Inclusion criteria (literature review)</b>	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
<b>Incremental analysis</b>	The analysis of additional costs and additional clinical outcomes with different interventions.
<b>Incremental cost</b>	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
<b>Incremental cost-effectiveness ratio (ICER)</b>	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
<b>Incremental net benefit (INB)</b>	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
<b>Indirectness</b>	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
<b>Intention to treat analysis (ITT)</b>	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
<b>Intervention</b>	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
<b>Intraoperative</b>	The period of time during a surgical procedure.
<b>Kappa statistic</b>	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
<b>Length of stay</b>	The total number of days a participant stays in hospital.
<b>Licence</b>	See 'Product licence'.
<b>Life-years gained</b>	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
<b>Likelihood ratio</b>	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
<b>Long-term care</b>	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
<b>Loss to follow-up</b>	People who have left the trial for an unknown reason.

<b>Markov model</b>	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
<b>Mesalazine</b>	A type of aminosalicylate. Also known as 'mesalamine'.
<b>Meta-analysis</b>	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
<b>Multivariate model</b>	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
<b>Negative predictive value (NPV)</b>	A measure of the usefulness of a prognostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
<b>Number needed to treat (NNT)</b>	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
<b>Observational study</b>	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case-control studies.
<b>Odds ratio</b>	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
<b>Opportunity cost</b>	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
<b>Outcome</b>	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
<b>P-value</b>	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
<b>Perioperative</b>	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
<b>Placebo</b>	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
<b>Polypharmacy</b>	The use or prescription of multiple medications.
<b>Positive predictive value</b>	A measure of the usefulness of a prognostic test. It is the proportion of

<b>(PPV)</b>	those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.
<b>Postoperative</b>	Pertaining to the period after patients leave the operating theatre, following surgery.
<b>Power (statistical)</b>	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
<b>Preoperative</b>	The period before surgery commences.
<b>Pre-test probability</b>	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
<b>Primary care</b>	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
<b>Primary outcome</b>	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
<b>Product licence</b>	An authorisation from the MHRA to market a medicinal product.
<b>Prognosis</b>	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
<b>Prospective study</b>	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
<b>Publication bias</b>	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found).
<b>Quality of life</b>	See 'Health-related quality of life'.
<b>Quality-adjusted life year (QALY)</b>	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
<b>Randomisation</b>	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even

	distribution of participants with different characteristics between groups and thus reduce sources of bias.
<b>Randomised controlled trial (RCT)</b>	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
<b>RCT</b>	See 'Randomised controlled trial'.
<b>Receiver operated characteristic (ROC) curve</b>	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
<b>Reference standard</b>	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
<b>Relative risk (RR)</b>	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
<b>Reporting bias</b>	See publication bias.
<b>Resource implication</b>	The likely impact in terms of finance, workforce or other NHS resources.
<b>Retrospective study</b>	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
<b>Review question</b>	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
<b>Secondary outcome</b>	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
<b>Selection bias</b>	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
<b>Sensitivity</b>	<p>Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects.</p> <p>See the related term 'Specificity'.</p>
<b>Sensitivity analysis</b>	<p>A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.</p> <p>One-way simple sensitivity analysis (uni-variate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.</p>

	<p>Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.</p> <p>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.</p> <p>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).</p>
<b>Significance (statistical)</b>	<p>A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 (<math>p &lt; 0.05</math>).</p>
<b>Specificity</b>	<p>The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases.</p> <p>See related term 'Sensitivity'.</p> <p>In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.</p>
<b>Stakeholder</b>	<p>Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.</p>
<b>Subacute ulcerative colitis</b>	<p>A manifestation of moderately to severely active ulcerative colitis that would normally be managed in an outpatient setting and that does not require hospitalisation or the consideration of urgent surgical intervention.</p>
<b>Systematic review</b>	<p>Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.</p>
<b>Time horizon</b>	<p>The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.</p>
<b>Treatment allocation</b>	<p>Assigning a participant to a particular arm of the trial.</p>
<b>Uni-variate</b>	<p>Analysis which separately explores each variable in a data set.</p>
<b>Utility</b>	<p>A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.</p>



## **13 List of appendices**

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**Appendix M: Research recommendations**

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