National Institute for Health and Clinical Excellence

Ulcerative Colitis
Scope Consultation Table
7 June 2011 - 5 July 2011

Type	Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Abbott laboratories UK	1	2.1 e	The scope suggests that in expert centres elective pan-proctocolectomy is associated with an operative mortality of between 1% and 4%, and postoperative lifelong morbidity of up to 15%. Given that these guidelines will be used across the UK and not just in expert centres, Abbott considers that it might be better to use the published literature for the likely morbidity in patients following a pan-proctocolectomy, otherwise this could be considered to be misleadingly low. For example evidence suggests that there is a 56-98% decrease in female fertility following surgery[i,ii,iii], which has substantial impact on quality of life. Furthermore, 1.5% of males are reported to become impotent[iv]. Between 10%-60% of UC patients develop pouchitis post surgery, 20% go on to have a small bowl obstruction and 4% develop pouch-vaginal fistulae. [v] A substantial number of patients having a pan-proctocolectomy will still have problems with urgency, leakage, nocturnal soiling, and some require conversion to a permanent ileostomy after ileal pouch-anal anastomasis failure.[vi] Therefore, Abbott suggests that this sentence is amended to better reflect the extent and seriousness of the complications associated with pan-proctocolectomy surgery.	Thank you. We have expanded on the complications associated with pan-proctocolectomy in the scope.
SH	Abbott laboratories UK	2	3.3	Abbott considers that it would be useful when discussing the management of UC that treatment options are discussed according to the severity of UC rather than just UC generally. The BSG guidelines for IBD published in *Gut* in 2011 state that therapeutic decisions depend on disease activity and extent, where disease activity is best evaluated objectively using a clinical activity index (Truelove and Witts or Mayo Clinic). For example, the guidelines state that for mild to moderate disease, mesalazine, an aminosalicylate, is recommended and evidence shows it is	Thank you for your comment. Different severities of the disease may be taken into account depending upon the evidence found.

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				effective. However for acute severe disease, intravenous corticosteroids, ciclosporin and infliximab are recommended. The reason being that the same therapy is not equally effective for all diseases severity categories and for these severe patients, aminosalicylates and the immunomodulators like azathioprine are considered completely ineffective and inappropriate treatment options.	
SH	Abbott laboratories UK	3	3.3.1	As discussed in comment 2 above, Abbott suggests that management of disease is dependent on severity and extent as per the BSG guidelines. Section 3.3.1 a) specifically discusses drug therapy for the induction and maintenance of remission for acute and severe exacerbations of UC, and includes the following drug categories: aminosalicylates, ciclosporin, corticosteroids, and immunomodulators – AZA and 6-MP. Abbott has a couple of concerns around this section of the scope. Firstly, as mentioned in comment 2, aminosalicylates and traditional immunomodulators are not used in acute severe exacerbations to induce or maintain remission – in fact, it is likely that patients having an acute flare will already be on these treatments and they are failing. Secondly, it should be made clear that ciclosporin and the immunomodulators azathioprine, 6-mercaptopurine and methotrexate are all unlicensed for the treatment of ulcerative colitis. If this section were split into drug therapy for the induction and maintenance of mild, moderate and severe UC separately then the different types of drug and the evidence to support their use can be discussed appropriately. Consequently, the anti-TNFs (adalimumab and infliximab) should also be included in the list of drug therapies for the induction and maintenance of remission for acute and severe exacerbations of ulcerative colitis being considered for the guidelines.	Thank you for your comment. The wording in the scope has been changed to: *drug therapy for the induction of remission for mild, moderate and severe active ulcerative colitis, and maintenance of remission.* The guideline development group will consider the different disease severities where evidence permits. We will cross refer to the technology appraisals TA140 and TA163.
SH	Abbott laboratories UK	4	3.4	Other outcomes which should be included for consideration in the list of main outcomes are : -Mucosal healing	Thank you. The scope lists the main outcomes that we will consider. When the guideline development group is

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				-Steroid-free remission -Work Productivity -CRP levels -Faecal Calprotectin levels -Complications of surgery, including fertility outcomes.	convened, specific outcomes for each review question will be agreed, and these will not be restricted to those listed in the scope. The guideline development group will decide which outcomes are appropriate for each review question.
SH	Abbott laboratories UK	5	4.1.2	It is our understanding that the review of NICE TAG140 – infliximab for subacute manifestations of ulcerative colitis, has been deferred until the completion of the GETAID CYSIF and CONSTRUCT trials, which are unlikely to complete in time for this clinical guideline.	Thank you. We will cross refer to TA140 in the guideline. It is not possible to delay the development of the guideline to wait for the publication of these trials.
SH	British Nuclear Medicine Society	1	3.3.2 b	Nuclear Medicine imaging with Tc99m HMPAO labelled white cells can assist in the differentiation between Crohn's disease and ulcerative colitis particular in the context of a pancolitis and can predict in the acutely unwell colitic when acute colectomy is needed.	Thank you for your comment. Diagnosis is out side of the remit of this guideline / quality standard, which covers the management of ulcerative colitis.
SH	British Nuclear Medicine Society	2	4.1.2 a	Serial nuclear medicine imaging with Tc99m HMPAO labelled white cells can predict treatment response to biological agents in a non-invasive manner and can be used as an adjutant to endoscopy if such is not possible. This should show earlier compared to changes in perfusion / hyperaemia with CT as it visualises the site of leucocytes in inflammation response (or not).	Thank you for your comment. This is outside of the remit.
SH	British Nuclear Medicine Society	3	4.1.3 c	F-18 FDG PET/CT could offer an adjutant to individual patients in whom neoplasm secondary to UC is strongly suspected but endoscopy is not possible due to fibrosis. There has been the suggestion that F-18 FDG PET/CT pneumocolon in bowel cancer offers a very accurate test for assessing potential dysplasia or neoplasia in polyps revealed on CT pneumocolon.	Thank you for your comment. This is outside of our remit.
SH	BSPGHAN	1	3.3.1	We are pleased to see children and young people included. Although the age ranges seem rather arbitrary, the division of pre- and peri/post-pubertal may have some benefit in discussion of growth, longer term maintenance therapies and choice of	Thank you. The age range was divided to separate younger children and children of pubertal age, in order to detect issues relating to puberty and

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				adult/paediatric surgeon. Children under age 5 have previously been singled out as a separate entity with potentially more aggressive disease and higher incidence of gene defects (e.g. IL-10R defect).	transition from paediatric to adult services. We have removed the age ranges from the scope. Children under five years old are a small group and it is not practical to consider a further subdivision.
SH	BSPGHAN	2	3.3. 1	We note the absence of biologics in the treatment of UC. Given the impending publication of data on anti-TNF and UC in children (prospective RCT in the manner of REACH study) this data should be addressed for validity and generaliseability. In paediatric practice there is considerable variation in prescribing practice of anti-TNFs in UC. b) Indications and timing of surgical management; for example: Acute Severe Colitis (ileoanal pouch surgery / total colectomy with ileostomy). The implications of pouch surgery on future fertility may be different for young adolescents and children compared to adults and consideration must be given for recommendations for counselling for timing for pouch surgery.	Thank you; we have noted your comments. We will refer to the relevant technology appraisals (TA140 and TA163) for adults. Infliximab for ulcerative colitis in children is currently being considered via NICE's topic selection process. Evidence for adverse effects of surgery on fertility will be considered and is specifically identified in the listed outcomes in section 3.4.
SH	BSPGHAN	3	4	This seems equally applicable to children and young people and is a very welcome extension of the usual guideline remit. There is no mention of reviewing the IBD Quality Standards of 2009, produced with broad collaboration of societies and patient groups. These standards formed the basis of the 3rd Round of the National Audit as well as the recently completed Quality Improvement Pilot study led by the BSG, from which data on both paediatric and adult centres should soon be available.	Thank you. It is anticipated that the NICE guideline will be the primary source for the NICE quality standard. Reviews of evidence from guidelines not developed by NICE may be considered by the Guideline Development Group if certain conditions are met. These are detailed in section 6.6.2 of the Guidelines Manual, available on the NICE website.
SH	BSPGHAN	4	7.3	There is now the paediatric organisational data available from the 3rd round of the National IBD Audit, with further data from this	Thank you; this has been noted.

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				round expected in early 2012. It seems logical to quote the most recent dataset.	
SH	CROHN'S and COLITIS UK	1	2.1 a	The incidence quoted is significantly higher than the figures generally quoted – presumably there is a reference for the numbers given.	Thank you. The prevalence figures in the scope have been changed to the figures quoted by the BSG guidelines.
SH	CROHN'S and COLITIS UK	2	2.1 e	Patients generally would not describe a pan-proctocolectomy as a cure. It can be an effective treatment eliminating the symptoms of severe UC but the patient then has to manage a stoma or live with an ileoanal pouch which has its own level of morbidity.	Thank you. The wording in the scope has been changed to: *Elective pan-proctocolectomy can be an effective treatment for eliminating the symptoms of severe ulcerative colitis. There is postoperative morbidity associated with stoma care and ileonal pouch use.*
SH	CROHN'S and COLITIS UK	3	2.1 f	It is worth noting that the risk applies to patients with extensive but quiescent disease. This means that patients who are living with a low level of symptoms and therefore not in active specialist follow-up may be at risk of CRC. IBD Services should extend to such patients to ensure they are in CRC surveillance programmes..	Thank you, we have noted your comment. People with ulcerative colitis at risk of colorectal cancer should be identified by colorectal cancer surveillance programmes. See '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
SH	CROHN'S and COLITIS UK	4	2.2	There should be a point (c) noting that the provision of 5ASA therapy has become a focus for cost-saving measures by PCTs and competition among pharmaceutical companies. There is concern that unilateral switching of patients 5ASA medication on cost not clinical grounds is becoming more frequent. Guidance is needed to protect the interests of patients (cf. the Crohn's and Colitis UK statement www.crohnsandcolitis.org.uk/)	Thank you. This issue is included and highlighted generally in section 2.2g.
SH	CROHN'S and COLITIS UK	5	3.3.1 a	There should be a reference to the importance of patient education and support in relation to maintenance therapy for UC. Adherence is a recognised problem.	Thank you. Patient education and support is already referred to in section 3.3.1 c) and encompasses the whole patient journey.
SH	CROHN'S and	6	3.3.2	We feel strongly that diagnosis should be included to ensure that	Thank you. We agree that diagnosis is

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	COLITIS UK		a	there is adequate NICE guidance on how best to identify possible UC in primary care.	important, but it is outside of the remit from the Department of Health, which is management of ulcerative colitis.
SH	CROHN'S and COLITIS UK	7	3.3.2 g	We propose that both leukapheresis and probiotics should be included as these are treatments of significant interest to patients and therefore it is important to have NICE Guidance.	Thank you. There was no strong feedback from stakeholders that that leukapheresis and probiotics should be included in the scope. As time is limited, we are unfortunately unable to include everything within the guideline, and we have decided to exclude this analysis. There is existing NICE interventional procedure guidance on leukapheresis for inflammatory bowel disease (IP126).
SH	CROHN'S and COLITIS UK	8	4.1.3	Diagnosis should be included – see above.	Thank you. We agree that diagnosis is important; however this is outside of our remit from the Department of Health, which is management of ulcerative colitis.
SH	Department of Health	1	General	The Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comments.
SH	Dr Falk Pharma UK Ltd	1	1.2	Will existing guidelines be the base for the NICE quality standard? For example, IBD guidelines of the British Society of Gastroenterology (Mowat 2011) and the IBD Standards 2009. These clinical guidelines are already published. The BSG guidelines refer to the NICE guidance, however, even in the prevalence figures (2.1.a), there are considerable discrepancies with the BSG guidelines. The correlation between existing guidance and the proposed NICE guidance is not clear.	Thank you. It is anticipated that the NICE guideline will be the primary source for the NICE quality standard. Reviews of evidence from guidelines not developed by NICE may be considered by the Guideline Development Group if certain conditions are met. These are detailed in section 6.6.2 of the Guidelines Manual, available on the NICE website.
SH	Dr Falk Pharma UK Ltd	2	2.2 b	The following comments relate only to 5-aminosalicylates and not other drug classes: 5-ASA and corticosteroids seem to be presented as equivalent	Thank you. The wording has been amended and now reads: *Treatment of relapse may depend on the clinical*

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				alternatives for the treatment of relapse. It should be made clear that 5-ASA, i.e., mesalazine, in adequate doses, considering also the option of concomitant use of oral and rectal preparations is the standard in the treatment of mild to moderate, acute inflammatory episodes, whereas corticosteroids are used for 5-ASA non-responders and severe episodes of inflammation.	*severity, extent of disease and patient preference and include the use of aminosalicylates or corticosteroids.*
SH	Dr Falk Pharma UK Ltd	3	3.3	Consideration should be given to different drug delivery mechanisms and formulations, which mean there are different recommended dosages for products and the different delivery systems mean that drug gets to different locations in the bowel where the disease is located. The relevance of targeting the release of the principally topically acting 5-ASA is obvious and broadly acknowledged with regard to treating inflammations with different extensions with different preparations via different routes, oral vs. rectal. In contrast, what is less well acknowledged is that targeting the release of a topically acting drug is also important with regard to oral preparations. Therefore the differences in the release characteristics should be considered (Forbes et al. Aliment Pharmacol Ther 2002; 17:1207-14) in individual patients. i.e. A patient who responded to a specific oral 5-ASA preparation may not necessarily show a similar response to another oral preparation and patients who did not show response to a specific preparation may respond to a different preparation.	Thank you; we have noted your comment. This will be considered by the guideline development group if appropriate evidence is identified during the literature search.
SH	Dr Falk Pharma UK Ltd	4	3.3	Issues on adherence to therapy should be included, considering also differences in dosing recommendations in the SmPC (e.g., single daily dose; relation with food, etc.). Adherence is relevant for maintenance of remission and in prophylaxis against CRC development. This issue should also acknowledge that patient knowledge and confidence (i.e., not to have frequent changes in product just for minor economic reasons) is an important issue.	Thank you. We will refer to the NICE medicines adherence clinical guideline CG76 as appropriate.
SH	Dr Falk Pharma UK Ltd	5	3.4 b	In looking at response and remission, mucosal healing should be considered as a measure of long term efficacy. Relevance of mucosal healing has also to be considered with regard to colorectal carcinomas see 2.1 f.	Thank you. The guideline development group will decide which outcomes are appropriate for each review question once the group has been convened.

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SH	Dr Falk Pharma UK Ltd	6	3.4 b	Response and remission should also include time to resolution of symptoms i.e., time to first resolution of clinical symptoms and at a later stage also mucosal healing.	Thank you. The guideline development group will decide which outcomes are appropriate for each review question once the group has been convened.
SH	Dr Falk Pharma UK Ltd	7	3.5	Costs should be reviewed in light of licensed drug dosage recommendations rather than looking at gram vs gram.	Thank you for your comment. This has been noted.
SH	Dr Falk Pharma UK Ltd	8	3.5	Costs should also take the CRC-preventive effects of continuous 5-ASA treatment into consideration.	Thank you. The GDG would consider CRC-preventive effects.
SH	Ferring Pharmaceuticals	1	1.2	Ferring Pharmaceuticals would like to draw your attention to our economic evaluations of Pentasa: *Connolly, M. Nielsen, S. Currie, C. Poole, C. Travis, S.* *An economic evaluation comparing once daily with twice daily mesalazine for maintaining remission based on results from a randomised controlled clinical trial.* *Journal of Crohn's and Colitis (2009) 3, 32–37* *Connolly, M. Nielsen, S. Currie, C. Marteau, P. Probert, C.Travis, S.* *An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-to-moderately active ulcerative colitis based on results from a randomised controlled trial* *Journal of Crohn's and Colitis (2009) 3, 168–174*	Thank you for highlighting these studies.
SH	Ferring Pharmaceuticals	2	2.2 f	We would highlight the BSG guidelines: "Maintenance therapy with all 5-ASA drugs may reduce the risk of colorectal cancer by up to 75% (OR 0.25, CI 0.13 to 0.48)." This references: *Eaden, J. Abrams, K. Ekbom, A. et. al. Colorectal cancer prevention in ulcerative colitis: a case-control study. Aliment Pharmacol Ther 2000;14:145e53.* Other studies showing this link include:	Thank you for highlighting this guidance.

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				Tang J, Sharif O, Pai C, Silverman AL. Mesalamine protects against colorectal cancer in inflammatory bowel disease. Dig Dis Sci. 2010. ;55(6):1696-703. Epub 2009 Aug 25.	
SH	Ferring Pharmaceuticals	3	2.2 b	Ferring Pharmaceuticals believes that a class effect of 5ASAs should not be assumed. 5ASAs vary in release mechanism, with site specific actions, and release profiles giving different colonic concentrations (Laursen 1990). Studies showing long term remission are performed independently, often with different inclusion/exclusion criteria and with different definitions of remission. *Staerk Laursen, L. Stokholm, M. Bukhave, K. Rask-Madsen J. and Lauritsen, K.* *Disposition of 5-aminosalicylic acid by olsalazine urinary excretion, colonic concentrations, serum values, and with ulcerative colitis: comparison of intraluminal and three mesalazine preparations in patients.* *Gut 1990;31;1271-1276* We would also draw your attention to our studies demonstrating Pentasa efficacy: *Marteau P, Probert C, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study.* *Gut 2005;54:960e5*. *Dignass AU, Bokemeyer B, Adamek H, et al.* *Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis.* *Clin. Gastroenterol. Hepatol. 2009;7:762e9*.	Thank you for your comments. This will be considered by the guideline development group when reviewing the evidence.
SH	Ferring Pharmaceuticals	4	2.2 g	We would draw your attention to the 2011 BSG "Guidelines for the management of inflammatory bowel disease in adults"; "Recommendations for the treatment of active (left-sided or extensive) ulcerative colitis:	Thank you for highlighting this reference. Aminosalicylates are included in the scope and any research evidence will be assessed against

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				Topical mesalazine combined with oral mesalazine >2 g/day is more effective than oral therapy alone for both left-sided and extensive colitis" *Marteau, P. Probert, C. Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut 2005;54:960e5.*	criteria for inclusion and quality in accordance with the NICE methodology.
SH	Ferring Pharmaceuticals	5	3.1.1 b	We would highlight the difficulties with compliance in 12-18 year olds. Ferring are introducing a patient compliance package.	Thank you; your comment has been noted.
SH	Ferring Pharmaceuticals	6	3.3.1 a	Again we highlight that 5ASAs are not interchangeable. We would also suggest considering splitting disease management into segments such as high or low disease or extensive and localised disease.	Thank you. This will be addressed when the guideline development group review the evidence.
SH	Ferring Pharmaceuticals	7	3.3.2 e	In light of your previous summary regarding the high rates of surgery occurring in UC patients, Ferring Pharmaceuticals believes that Pouchitis should be included within this scope. The colectomy rate for UC patients is around 30% (Jess *et. al.* 2006). There is a 46% incidence of Pouchitis in patients who have undergone proctocolectomy with ileal pouch-anal anastomosis. Pouchitis therefore affects a significant number of UC patients (approximately 15%). *Jess, T. Loftus, E. Jr, Velayos, F. et. al.* *Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted county, Minnesota. Gastroenterology. 2006;130:1039 –1046.* *Ferrante, M. Declerck, S. De Hertogh, G. et. al.* *Outcome after proctocolectomy with ileal poucheanal anastomosis for ulcerative colitis.* *Inflamm. Bowel Dis 2008;14:20e8.*	Thank you. Pouchitis is a different clinical condition and is outside of our remit, which is the management of ulcerative colitis.

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SH	Ferring Pharmaceuticals	8	4.1.1 d	Ferring would stress the need for continuing therapy even when in remission. We are producing patient compliance materials to aid this.	Thank you; we have noted your comment.
SH	Medicines and Healthcare product Regulatory Agency (MHRA)	1	2.2 b	Use of '5-aminosalicylic acid' can cause ambiguity. Strictly, the compound 5-aminosalicylic acid is mesalazine; the other aminosalicylates (balsalazide, olsalazine, and sulfasalazine) are combinations of 5-aminosalicylic acid with other moieties (another molecule of 5-aminosalicylic acid, in the case of olsalazine)	Thank you. *5-aminosalicylic acid* has been changed to *aminosalicylates* in the scope.
SH	Medicines and Healthcare product Regulatory Agency (MHRA)	2	2.2 d	The approved names of drugs should **not** be abbreviated—abbreviations lead to errors (which, in the case of azathioprine and mercaptopurine, can be dangerous) The correct approved name is 'mercaptopurine', **not** '6-mercaptopurine'; use of figures in drug names can lead to errors in dosage and supply	Thank you. All abbreviations have been replaced with the full drug names.
SH	Medicines and Healthcare product Regulatory Agency (MHRA)	3	3.3.1 a	In December 2008 NICE issued guidance on the use of infliximab for acute exacerbations of ulcerative colitis, but this category of drugs is not included in the key management areas to be covered (but it is mentioned in section 2.2f and section 4.1.2a).	Thank you; we have noted your comments. We have changed the wording of the scope so that it refers to anti-TNF agents. We will cross refer to the relevant technology appraisals (TA140 and TA163).
SH	Medicines and Healthcare product Regulatory Agency (MHRA)	4	3.3.1 a	When any recommendation for the use of a medicine falls outside the marketing authorisation, this should be clearly stated and an explanation given on how this affects the clinician's responsibility	Thank you; we have noted your comments.
SH	Merck Sharp & Dohme Limited	1	2.2 f	This section states that newer agents such as the anti-TNF infliximab, and more recently adalimumab, have provided an alternative to ciclosporin in the management of acute severe colitis over the past few years. It should be noted that adalimumab is not licensed for use for the treatment of ulcerative colitis (and has no data supporting use in this patient population) and thus should NOT be considered an alternative.	Thank you. The wording of the scope has been changed. It now reads: Anti-TNF agents have been used as an alternative to ciclosporin for managing acute severe colitis over the past few years.
SH	Merck Sharp &	2	2.2	The section limits the description of use of infliximab to the acute-	Thank you. The use of infliximab in this

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	Dohme Limited		f	severe patient population. MSD would kindly note that the pivotal clinical trials and the majority of data on the use of infliximab n ulcerative colitis are for the moderately-to-severely active patient (versus the acute severe population). Therefore, MSD would suggest the mention of infliximab for use in the moderately-to-severely active patient as well (currently described as the "sub-acute" patient) As reference, please note that: Infliximab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Infliximab now has 5yrs of licensed experience in UC having gained its license in March 2006	population is covered by the technology appraisal TA140 and this will be cross-referred to in the guideline.
SH	Merck Sharp & Dohme Limited	3	2.2 f	There is also evidence to show that there are benefits of using infliximab earlier in therapy. I. ACT 1 and ACT2. At the time of enrolment, 98% of subjects had a history of treatment with corticosteroids, 74% had received immunomodulatory agents, and 98% had received 5-ASA compounds. That means that 26% were 6-MP or AZA naïve. ACT1 and ACT2 results did show that as compared with patients who received placebo, patients who received infliximab were significantly more likely to have a clinical response and be in clinical remission at weeks 8 and 30 in both trials and in week 54 in ACT 1. Similarly, patients who received infliximab were significantly more likely to have mucosal healing at weeks 8 and 30 in both trials and in week 54 in ACT 1. Proven efficacy of infliximab and the presence of 26% immunomodulator naïve patients at enrolment imply that the treatment with infliximab could start earlier - before the administration of immunomodulator agents (6-MP or AZA).	Thank you for highlighting these trials. The use of infliximab to treat ulcerative colitis is covered by the technology appraisals TA140 and TA163, and these will be cross-referred to in the guideline.

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				II. SUCCESS study. At baseline 90% of the patients were immunomodulator naïve. The SUCCESS study results did show that infliximab +AZA regimen was superior to AZA and infliximab monotherapy in inducing steroid-free remission in patients with moderate-severe UC. The results of the study imply that infliximab can be used effectively in combination with AZA earlier on in the course of treatment. III. Paediatric UC. The results of OP747 study (Hyams et al) (presented in an oral presentation at this years DDW (May 2011)) showed that infliximab induced clinical response in 73 percent of patients aged 6-17 years at week 8 - the primary endpoint of the trial. Also at week 8, 40 percent of patients were in clinical remission by the Mayo score and 33.3 percent were in remission by the Paediatric UC Activity Index (PUCAI). In addition, 68.3 percent of patients achieved mucosal healing at week 8. MA for the paediatric UC is expected Q4 2011. (It should be noted that in the SUCCESS and OP747 study infliximab was used off label (although approved for use in moderate to severe adult UC – the patients have to have an inadequate response to corticosteroids and 6-MP or azathioprine (AZA), or be intolerant to, or have medical contraindications for such therapies), however adalimumab and ciclosporin are both mentioned in the scoping and are not licensed in UC).	
SH	Merck Sharp & Dohme Limited	4	2.2 a	Presently the two main medical alternatives to surgery are cyclosporin and infliximab. A national randomised control trial is presently being performed to compare the two in this acute scenario (CONSTRUCT). The results are expected to support the French data presented at this years AGA in their CYSIF trial. Essentially this demonstrated similar efficacy at day 7 (ciclosporin 84% Vs infliximab 86% remission), although the cyclosporin group suffered significantly more side effects. Intravenous ciclosporine can induce remission in patients with severe steroid-refractory ulcerative colitis, but its use is	Thank you. The scoping group is aware of these trials. The results of these trials will be considered when the technology appraisal TA163 is reviewed. The guideline will cross refer toTA163.

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				controversial because of toxicity and long-term failure.(Cima RR, 2005;Lichtenstein GR,2006, Kornbluth A, 2004). It should be pointed out that surgery is not without its side effects and complications, and certainly should not be seen as a curative procedure. Typical post-surgical problems include persistent increased stool frequency (3-10 x/day), bile acid malabsorption, small bowel obstruction (20%), pouchitis (40%), fistulae (4%), strictures (9-19%), abscesses (5-12%), impotence (1.5%) and decreased fertility (56%) (Sager PM. IBD. 2003; 491-511). CYSIF was first presented at ECCO in Feb 11 and again at DDW in May 11.	
SH	Merck Sharp & Dohme Limited	5	2.2	MSD would stress that colectomy, although beneficial for some is not a cure and comes with a number of potential problems that impact the patients' quality of life significantly and have additional cost implications in through corrective measures. (P Sagar, 2003). I.e. it is estimated that between 10-60% experience pouchitis. In current practice, TPC with IPAA is the method of choice for most patients. Even with surgical advances, IPAA remains a technically difficult operation associated with significant morbidity. IPAA is associated with an early morbidity rate of 30% and a 3-12% long-term risk of pouch failure (McGuire BB, 2007; Bach SP, 2006; Shen B, 2005). A significant proportion of IPAA receivers will experience complications including small-bowel obstruction, pouch leak, pelvic sepsis, anastomotic stricture, or pouch fistula, pouchitis, pouch failure, incontinence, and reduced fecundity in women (Cima RR, 2005; Bach, SP 2006;Shen B, 2005).	Thank you. We have changed the wording of the scope. It now reads: *Elective pan-proctocolectomy can be an effective treatment for eliminating the symptoms of severe ulcerative colitis. There is postoperative morbidity associated with stoma care and ileonal pouch use* We have expanded on the complications associated with pan-proctocolectomy in the scope.
SH	Merck Sharp & Dohme Limited	6	3.1.1 c	As stated in comment 5, colectomy can result in reduced fecundity and thus the potential impact on young woman should be given consideration. The IBSEN group have developed a risk matrix model for prediction of colectomy in ulcerative colitis patients. The matrix depicts important differences in the risk of colectomy among patient groups, being almost 15 times higher in the highest	Thank you; your comment has been noted.

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				compared to the lowest risk group. (M. Cvancarova, C. Solberg, M. Vatn, B. Moum, on behalf of IBSEN. OP161 RISK MATRIX MODEL FOR PREDICTION OF COLECTOMY IN A POPULATION BASED STUDY OF ULCERATIVE COLITIS PATIENTS. THE IBSEN STUDY UEGW 2010). This could provide a useful tool to stratify patient groups by risk and provide the best possible care tailored to specific patient groups.	
SH	Merck Sharp & Dohme Limited	7	3.1.1 a	While Infliximab is not licensed for the management of acute severe ulcerative colitis in children, two recent articles would indicate that infliximab should be considered as a medical rescue therapy as an alternative to ciclosporin in this population. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN.Am J Gastroenterol. 2011 Apr;106(4):574-88. Epub 2011 Jan 11 Turner D and Griffiths A. Acute severe ulcerative colitis in children: a systematic review.Inflamm Bowel Dis. 2011 Jan;17(1):440-9	Thank you for highlighting these studies.
SH	Merck Sharp & Dohme Limited	8	3.1.1 b	Infliximab has demonstrated efficacy in the treatment of paediatric patients with UC. MSD have submitted this to the regulatory authorities via a centralised process and anticipate positive opinion from the CHMP on 21st July.	Thank you; your comment has been noted.
SH	Merck Sharp & Dohme Limited	9	3.3.1 a	MSD would strongly suggest that infliximab, the only licensed biologic for the treatment of UC, be included in this section of the draft scope and thus also be included in the clinical guideline, as it is a commonly used treatment for ulcerative colitis in UK clinical practice. Infliximab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-	Thank you. We will cross refer to the technology appraisals TA140 and TA163.

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				mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	
SH	Merck Sharp & Dohme Limited	10	3.4	The most widely used Health-Related Quality of Life (HRQL) measures are the generic preference based measures EQ-5D and SF-36. The condition specific measure IBDQ is used less widely, with more use seen in trials than in clinical practice.	Thank you. HRQOL would be measured with NICE's preferred measure- EQ5D, as well as other generic or relevant condition specific measures (e.g. IBDQ) where studies permit. The GDG would make the final decision about particular QOL instruments.
SH	Merck Sharp & Dohme Limited	11	4	As was discussed at the scoping workshop, MSD supports the suggested move to cover separate patient populations under the remit of the Quality Standard, i.e. in order to differentiate between patients with mild to moderate ulcerative colitis and moderate to severe.	Thank you for your comment. Disease severity will be considered by the guideline development group where evidence permits.
SH	Merck Sharp & Dohme Limited	12	4.1.2 a	MSD believes that biologics (as other medicines in the same class) should be examined like for like: infliximab and adalimumab should be examined under the same definitions of patient populations: either "acute and sub-acute" or " moderate-severe".	Thank you. We are not able to address infliximab and adalimumab within the clinical guideline due to the existence of the technology appraisals. We will cross refer to the technology appraisals TA140 and TA163 in the guideline.
SH	NHS Direct	1	General	NHS Direct welcome the guideline and have no comments on the draft scope.	Thank you for your comments.
SH	Primary Care Society for Gastroenterology	1	1 f	Probably best to stress the cancer risk with longstanding extensive disease. Proctitis has very little if any increased risk.	Thank you. Cancer risk and the relationship with long standing extensive disease is already noted within the scope (section 2.1f).
SH	Primary Care Society for Gastroenterology	2	4.1.1	It would be worth exploring the use of shared care between primary and secondary care covering well controlled colitis and the provision of fast track clinics when such patients relapse.	Thank you for your comment. Diagnosis is outside of the remit, so shared care for diagnostic purposes will not be covered. Indications for drug treatment for relapse will be included if the evidence permits.
SH	Royal College	1	General	These guidelines will be welcome for a condition with such serious	Thank you for your comments.

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	General Practitioners			outcomes. In primary care increasingly being asked to maintain prescriptions for azathioprine etc	
SH	Royal College of Nursing		2.2 a	***Newer agents such as the anti-TNF infliximab and more recently adalimumab have provided an alternative to ciclosporin in the management of acute severe colitis over the past few years***: This nod towards the use of Infliximab in ulcerative colitis (UC) is not really supported other than in its use as rescue therapy when ciclosporin is not safe to use (NICE guidelines) and we are not aware of any good evidence for adalimumab in UC. In view of this, we would suggest that the above statement should be worded to reflect this variance rather than the suggestion that these are good alternatives, which is yet to be proven.	Thank you. The wording of the scope has been changed. It now reads: Anti-TNF agents have been used as an alternative to ciclosporin for managing acute severe colitis over the past few years.
SH	Royal College of Nursing		3.3.1 a	There is also then no mention of these medications (infliximab and adalimumab) in 3.3.1 a, where their use might be described as with the other medications. In view of the fact that this is at the beginning of the document we consider that its inclusion or at least the wording needs to be considered.	Thank you. The wording of section 2.2a has been revised.
SH	Royal College of Paediatrics and Child Health	1	3.1.1	We are pleased to see children and young people included. Although the age ranges seem rather arbitrary, the division of pre- and peri/post-pubertal may have some benefit in discussion of growth, longer term maintenance therapies and choice of adult/paediatric surgeon. Children under age 5 have previously been singled out as a separate entity with potentially more aggressive disease and higher incidence of gene defects (e.g. IL-10R defect).	Thank you. The age range was divided to separate younger children and children of pubertal age, in order to detect issues relating to puberty and transition from paediatric to adult services. We have removed the age ranges from the scope. Children under five years old are a small group and it is not practical to consider a further subdivision.
SH	Royal College of Paediatrics and Child Health	2	3.3.1	We note the absence of biologics in the treatment of UC. Given the impending publication of data on anti-TNF and UC in children (prospective RCT in the manner of REACH study) this data should be addressed for validity and generaliseability. In paediatric practice there is considerable variation in prescribing practice of	Thank you; we have noted your comments. We will refer to the relevant technology appraisals (TA140 and TA163) for adults. Infliximab for ulcerative colitis in children is currently

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				anti-TNFs in UC.	being considered via NICE's topic selection process.
SH	Royal College of Paediatrics and Child Health	3	3.3.1 b	The implications of pouch surgery on future fertility may be different for young adolescents and children compared to adults, and consideration must be given for recommendations for counselling for timing for pouch surgery.	Thank you; we have noted your comment and agree. Evidence for adverse effects of surgery on fertility will be considered and is specifically identified in the listed outcomes in section 3.4.
SH	Royal College of Paediatrics and Child Health	4	4	This seems equally applicable to children and young people and is a very welcome extension of the usual guideline remit.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	5	4	There is no mention of reviewing the document, *Quality Care: Service Standards for the healthcare of people who have Inflammatory Bowel Disease* (2009), which was produced with a broad collaboration of societies and patient groups. These standards formed the basis of the 3rd round of the National Audit, as well as the recently completed Quality Improvement Pilot study led by the British Society of Gastroenterology, from which data on both paediatric and adult centres should soon be available.	Thank you. It is anticipated that the NICE guideline will be the primary source for the NICE quality standard. Reviews of evidence from guidelines not developed by NICE may be considered by the Guideline Development Group if certain conditions are met. These are detailed in section 6.6.2 of the Guidelines Manual, available on the NICE website.
SH	Royal College of Paediatrics and Child Health	6	7.3	There is now the paediatric organisational data available from the 3rd round of the National IBD Audit, with further data from this round expected in early 2012. It seems logical to quote the most recent dataset.	Thank you; this has been noted.
SH	Royal College of Paediatrics and Child Health	7	General	Inflammatory bowel disease (IBD) is associated with an increase risk of fracture including vertebral crush fractures. Other evidence of significant bone disease in ulcerative colitis (UC) comes from biochemical (including vitamin D status), dual energy x-ray absorptiometry (DXA) and bone biopsy data. These are significant adverse consequences that result from both the condition and its treatment and which will have effects on the individual in both the short and long term. Additionally, the presence or occurrence of crush fractures (or other fragility fractures) may, in some cases, influence the choice of treatment of UC.	Thank you for your comments. We will include monitoring of bone health. We have included a paediatric consultant and nurse specialist in the GDG membership.

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				Identification and anticipation of skeletal problems is often done using DXA scanning. The International Society for Clinical Densitometry published a position statement in 2008 (authors included a number of our group) that highlighted the risk of fracture in IBD and covered the use of DXA scanning at presentation and as a tool for monitoring bone health. Maintenance of skeletal health is particularly important in childhood chronic disease. Childhood is clearly characterised by bone growth and bone mineral acquisition. Puberty is a crucial period of bone mineral acquisition and any perturbation of mineral acquisition during this time is harmful, potentially for a lifetime. We would expect that any quality standards for the management of UC would include some attention to skeletal health. Growth is included as an outcome but will depend on the health of bones, e.g. poor spinal growth due to crush fractures. As a more general point, it is strange to omit skeletal health from the scope of the work whilst including growth and pubertal development. The three are closely interlinked. "Adverse events" are also included as an outcome in the scope document. As fractures and osteopaenia/osteoporosis are adverse outcomes of both the condition and the treatment employed, it would make sense to bring them into the scope of the guidelines, particularly as their identification may in some cases influence the choice of treatment for the colitis. Elements that we suggest ought to be considered as being within the scope of the guideline are: • Assessment and optimisation of vitamin D status and calcium intake. • Monitoring for low bone mineral density/low bone mass with DXA.	

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				• Assessment with DXA and lateral spine radiographs in the event of localised bone pain or fragility fractures. We would also suggest that a paediatric endocrinologist with an interest in bone is formally involved in the process of developing these guidelines.	
SH	Royal College of Paediatrics and Child Health	8	general	**References to above comment:** Bishop N, Braillon P, Burnham J, Cimaz R, Davies J, Fewtrell M, Hogler W, Kennedy K, Mäkitie O, Mughal Z, Shaw N, Vogiatzi M, Ward K, Bianchi ML. Dual-energy X-ray aborptiometry assessment in children and adolescents with diseases that may affect the skeleton: the 2007 ISCD Pediatric Official Positions. J Clin Densitom. 2008 Jan-Mar;11(1):29-42. Fayez KG and Pawel RK. Advances in the understanding of mineral and bone metabolism in inflammatory bowel diseases. Am J Physiol Gastrointest Liver Physiol 300: G191–G201, 2011 Ward LM, Rauch F, Matzinger MA, Benchimol EI, Boland M, Mack DR. Iliac bone histomorphometry in children with newly diagnosed inflammatory bowel disease. Osteoporosis Int 2010 Feb;21 (2):331-7 F J Cowan, J T Warner, F D J Dunstan, W D Evans, J W Gregory, H R Jenkins. Inflammatory bowel disease and predisposition to osteopenia. Archives of Disease in Childhood 1997;76:325–329 Gokhale R, Favus MJ, Karrison T, Sutton MM, Rich B, Kirschner BS. Bone mineral density assessment in children with inflammatory bowel disease. Gastroenterology 1998;114:902–911 A M Boot, J Bouquet, E P Krenning,S M P F de Muinck Keizer-Schrama. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut 1998;42:188–194	Thank you.

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SH	The British Dietetic Association	1	General	We have circulated this consultation to our membership and we do not have any comments at this stage.	Thank you for your comments.
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	1	2.1	The number of UC patients quoted seems a lot. BSG article says 240,000 IBD pts in total with 146,000 UC. Here they are quoting 300,000.	Thank you. The prevalence figures in the scope have been changed to the figures quoted by the BSG guidelines.
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	2	2.2 d	6-MP needs to be changed to mercaptopurine, consistent with CD scope and to minimise error.	Thank you. 6-MP has been changed to mercaptopurine.
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	3	2.2 f	Adalimumab awaiting to licence	Thank you. Adalimumab has been removed from the scope and we have used the term *anti-TNF agents.*
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	4	3.3.1 a	They only seem to describe management of acute and severe exacerbations. Is mild and moderate disease not being included?	Thank you. Mild and moderate disease are included. The wording in the scope has been changed to: *drug therapy for the induction of remission for mild, moderate and severe active ulcerative colitis, and maintenance of remission.*
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	5	3.3.2 f	Osteopenia is being considered in CD. Consistency?	Thank you. We will include monitoring of bone health.
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	6	3.4 b	Response or remission - how are they measuring outcomes? Scales were defined in CD scope i.e. CDAI, PCDAI, HBI. Truelove and Witts criteria?	Thank you. The scope does not list specific indices for measuring response and remission, as these will be decided by the guideline development group. We are in close contact with group developing the Crohn's guideline to ensure consistency.
SH	United Kingdom Clinical Pharmacy Association	7	3.4 d	How is health related QL measured - consistency with CD scope - IBDQ, IMPACT?	Thank you. HRQOL would be measured with NICE's preferred measure- EQ5D, as well as other generic or relevant

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	(UKCPA)				condition specific measures (e.g. IBDQ) where studies permit. The GDG would make the final decision about particular QOL instruments.
SH	United Kingdom Clinical Pharmacy Association (UKCPA)	8	7.3	3rd round of audit now available.	Thank you; this has been noted.
SH	Vifor Pharma	1	General	The prevalence of iron deficiency in UC (IBD) patients is very high and ranges from 36%–90%, with a mean value of 45%, which underlines the fact that this condition may be considered the rule more than the exception. Gisbert J., Am J Gastroenterol. 2008;103:1299–1307. 'After attending to any discovered underlying cause, the aim of treatment should be to restore Hb concentrations and red cell indices to normal, and replenish iron stores'. BSG guidelines on IDA. Goddard Gut May 2011.	Thank you. Anaemia is a manifestation of many chronic conditions, not just ulcerative colitis. The management of anaemia as a result of ulcerative colitis is the same as for anaemia caused by other chronic conditions. It is not possible to address everything relevant to ulcerative colitis within this guideline.
SH	Vifor Pharma	2	General	Long-term prevention of anaemia by treatment of underlying IBD is primary but iron replacement is also needed and improves quality of life. Vijverman A, Piront P, Belaiche J, et al. Evolution of the prevalence and characteristics of anemia in inflammatory bowel diseases between 1993 and 2003. Acta Gastroenterol Belg 2006;69:1e4.	Thank you. Anaemia is a manifestation of many chronic conditions, not just ulcerative colitis. The management of anaemia as a result of ulcerative colitis is the same as for anaemia caused by other chronic conditions. It is not possible to address everything relevant to ulcerative colitis within this guideline.
SH	Vifor Pharma	3	General	Anaemia is a common complication of IBD. Comprehensive guidelines have recently been published from an expert working group. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis 2007;13:	Thank you. Anaemia is a manifestation of many chronic conditions, not just ulcerative colitis. The management of anaemia as a result of ulcerative colitis is the same as for anaemia caused by other chronic conditions. It is not possible to address everything relevant to ulcerative colitis within this guideline.
SH	Vifor Pharma	4	General	Despite the positive stance in many guidelines referenced in comments 1 and 3 above and others (E.g. Guidelines for the	Thank you. Anaemia is a manifestation of many chronic conditions, not just

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				management of inflammatory bowel disease in adults – March 2011) on the importance of treatment of Iron deficiency anaemia (IDA) it is poorly managed by most UK centres in paediatrics and adults as highlighted in a recent UK audit article. Prevalence and Management of Anemia in Children, Adolescents, and Adults with Inflammatory Bowel Disease. IBD May 2011.	ulcerative colitis. The management of anaemia as a result of ulcerative colitis is the same as for anaemia caused by other chronic conditions. It is not possible to address everything relevant to ulcerative colitis within this guideline.
SH	Vifor Pharma	5	3.4 d	Dr C Wells looked at QOL in anaemic IBD patients and concluded that 'Treatment of IBD-associated anemia with iron may lead to improvement in patients' QOL. Wells C., Inflamm Bowel Dis _ Volume 12, Number 2, February 2006	Thank you for highlighting this study. Anaemia is a manifestation of many chronic conditions, not just ulcerative colitis. The management of anaemia as a result of ulcerative colitis is the same as for anaemia caused by other chronic conditions. It is not possible to address everything relevant to ulcerative colitis within this guideline.
SH	Vifor Pharma	6	3.4 h	Treating pre operative anaemia is promoted by the Department of Health Enhanced Recovery Programme document from March 2010. In a study of 23,348 undergoing GI surgery, Leichtle found that 'Compared with non anaemic patients, those with severe, moderate and mild anaemia were more likely to have the adverse composite outcomes. Patients with a normal haematocrit had a reduced length of stay compared with anaemic patients. J Am Coll Surg 2011:212;187-194.	Thank you for highlighting this document; we have noted your comment.
SH	Warner Chilcott UK Ltd	1	2.1 a	What reference have you used to report current numbers in the UK? The new BSG guidelines [*Mowat C, Cole A, Windsor A, et al. Gut (2011). doi:10.1136/gut.2010.224154]* report the prevalence of ulcerative colitis in the UK " 243/100 000=146 000 people in UK population of 60 million"	Thank you. The prevalence figures in the scope have been changed to the figures quoted by the BSG guidelines.
SH	Warner Chilcott UK Ltd	2	2.2 b	In addition to clinical severity, treatment of relapse may depend on a variety of factors including **extent of disease and patient preference**.	Thank you. The wording has been amended and now reads: *Treatment of relapse may depend on the clinical severity, extent of disease and patient preference and include the use of aminosalicylates or corticosteroids.*

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SH	Warner Chilcott UK Ltd	3	2.2 b	A number of different 5-ASA preparations are available for the treatment of ulcerative colitis. Warner Chilcott would also like to remind NICE that the mesalazines are modified release preparations, and due to differing release profiles are not interchangeable and hence need to be recommended by brand.	Thank you for your comments. This will be considered by the guideline development group when reviewing the evidence. NICE clinical guidelines do not recommend specific brands.
SH	Warner Chilcott UK Ltd	4	2.2 c	A number of different 5-ASA preparations are available for the maintenance of remission of ulcerative colitis. Warner Chilcott would also like to remind NICE that the mesalazines are modified release preparations, and due to differing release profiles are not interchangeable and hence need to be recommended by brand.	Thank you for your comments. This will be considered by the guideline development group when reviewing the evidence. NICE clinical guidelines do not promote specific brands.
SH	Warner Chilcott UK Ltd	5	2.2 c	The statement "The majority of patients receive maintenance therapy with 5-ASA" should be replaced with **"Long-term maintenance therapy is generally recommended for all patients"** based upon the new BSG guidelines [*Mowat C, Cole A, Windsor A, et al. Gut (2011). doi:10.1136/gut.2010.224154]*	Thank you. The wording of the scope has been changed in response to the comment from the MHRA. It now reads*: The majority of patients receive maintenance therapy with aminosalicylates.*
SH	Warner Chilcott UK Ltd	6	7.3	The 3rd round of the Inflammatory Bowel Disease audit is now available on the Royal College of Physicians website. http://www.rcplondon.ac.uk/sites/default/files/report-of-the-results-for-the-national-organisational-audit-of-adult-inflammatory-bowel-disease-services-in-the-uk-2011.pdf	Thank you; this has been noted.

[i] Olsen, KO, et al. *Gastroenterology*. 2002;**122**:15-19.
[ii] Johnson P, et al. *Dis Colon Rectum.* 2004;**47**;1119–1126
[iii] Gorgun E, et al. *Surgery*. 2004;**136**(4):795–803
[iv] Pemberton JH, et al. *Ann. Surg.* 1987;**206**(4):504-513
[v] Sagar PM, Pemberton JH. Satsangi J, Sutherland L, et al,. *Inflammatory Bowel Diseases.* 2003:491-511.
[vi] Lichenstein G et al. *J clin Gasterenterol* 2006;**40**(8):669