

National Institute for Health and Clinical Excellence

Ulcerative colitis
Guideline Consultation Comments Table
21 January 2013 – 4 March 2013

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	AbbVie Ltd	1	Full	19	19	AbbVie considers that the following bullet point should be added under " <i>Related NICE Technology Appraisals</i> ": Adalimumab for the treatment of moderate to severe ulcerative colitis. TA 262 terminated appraisal. Available from: http://publications.nice.org.uk/adalimumab-for-the-treatment-of-moderate-to-severe-ulcerative-colitis-terminated-appraisal-ta262	Thank you for your comment. We have added the adalimumab TA262 terminated appraisal to this section.
SH	AbbVie Ltd	2	Full	50	7	AbbVie considers that the below wording should be amended to also include adalimumab: " <i>3. What are the benefits, risks and cost effectiveness of methotrexate, ciclosporin, tacrolimus, infliximab and adalimumab compared with each other and with placebo for induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids?</i> "	Thank you for your comment. Adalimumab has been added to the research recommendation.
SH	British Nuclear Medicine Society	1	Full	General		We acknowledge that the guidelines relate to management of ulcerative colitis and related interventions secondary to this.	Thank you for your comments. We agree with the first point but diagnosis was beyond the remit of the scope.

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						<p>Nuclear medicine is a physiological method of imaging and is often used in conjunction with other imaging CT, US, MRI, barium and plain radiographs in the initial diagnosis of ulcerative colitis. The NM test most commonly used is the Tc99m HMPAO labelled white cell study.</p> <p>This also has a proven role in the assessment of response to various medical interventions both biologicals (i.e. monoclonal therapy) and more conventional therapy.</p> <p>Bennick et al 'Evaluation of early treatment response and predicting the need for colectomy in active ulcerative colitis with 99mTc-HMPAO white blood cell scintigraphy' J Nucl Med 2004: 45; 1698-794.</p> <p>The immuno-modulation and monoclonal agents have a risk of sepsis and such white cell imaging has a role in searching for the underlying source, often when conventional imaging has been negative. I can not readily appreciate an estimate of the rate of this complication in the full guidance.</p>	<p>In relation to the second point, the GDG did not identify the NM test as one of the main outcomes in the reviews to demonstrate the efficacy of interventional treatments and to support their decision-making when formulating recommendations on treatments. The outcomes the GDG identified are listed in the protocols for the induction and maintenance of remission in Appendix C of the main guideline. Usually the GDG decide on seven outcomes for each review. Outcomes that directly measure effectiveness and are identified as important to patients (for example remission) are given priority over other outcomes that are considered to provide less direct evidence.</p> <p>In relation to the third point regarding biologics (monoclonal therapy), these have been reviewed by NICE in TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders</p>

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							<p>justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal, including other tumour necrosis factor (TNF) alpha inhibitors, and the terminated appraisal 'Adalimumab for the treatment of moderate to severe ulcerative colitis (TA262). NICE will also request a referral for an appraisal of golimumab for ulcerative colitis to be included in this multiple technology appraisal. See http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side by side with the recommendations in the clinical guideline in the NICE Pathway.</p> <p>Rates of sepsis Adverse events and serious adverse events were identified as outcomes in the reviews that evaluated the immunomodulators. Sepsis was not identified as a specific outcome measure but where appropriate specific serious adverse events are commented on (see section 5.43.1 where one case of mortality from sepsis was reported). The reviews did not evaluate the role of</p>

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							different diagnostic modalities of identifying complications.
SH	British Nuclear Medicine Society	2	Full	46 & 175	22 & 14	Plain abdominal radiograph, the finding described are of acute colitis likely to need acute surgery, I doubt that a surgeon would operate without cross-sectional imaging such as CT and hence economic case would need to be able cover CT in at least the proportion expected to have surgery	Thank you for your comment. The GDG do not agree with the view that people with acute colitis who are likely to need surgery would require a CT scan routinely prior to surgery. In addition a CT scan or the results of a CT scan was not included in the risk tools assessed. The risk factors listed are variables listed in the risk tools included in the review.
SH	British Nuclear Medicine Society	3	Full	14	23	See paper	Thank you for your comment.
SH	British Nuclear Medicine Society	4	Full	195	22	Re BMD ie DEXA often performed in NM departments and or medical physics department correctly refer onto osteoporosis guidelines	Thank you for your comment.
SH	British Nuclear Medicine Society	5	Full	170	10	Just to remind you that white cells have role in prediction of when medical treatment may fail and hence when surgery needed.	Thank you for your comment.
SH	British Society of Gastroenterology	1	Full	general		Heparin, or low-molecular weight heparin, should be added to the management of all in-patients being treated by severe UC; this is over and above the RCP-recommendations of VE prophylaxis.	<p>Thank you for your comment. The GDG agree this is an important part of the management of in-patients being treated for severe UC. However the use of heparin for VTE prophylaxis was not part of the scope.</p> <p>The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then</p>

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							<p>opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.</p> <p>At the stakeholder workshop, it was acknowledged that heparin addressed the complications of ulcerative colitis rather than the disease and was not prioritised for inclusion in the scope. As the use of heparin was not reviewed the GDG could not make a recommendation.</p> <p>However NICE 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 VTE in combination with the expectation of ongoing reduced mobility relative to their normal state while in hospital. This has been referred to in section 5.46 (Recommendation and link to evidence; other considerations).</p>
SH	British Society of Gastroenterology	2	Full	general		In-patients being treated for severe UC should be jointly managed by a gastroenterologist and coloproctologist, preferably with an interest in IBD.	<p>Thank you for your comment. Recommendation 1.1.12 (now 1.2.10) makes it clear that people with severe UC should be jointly managed by a gastroenterologist and colorectal surgeon. The GDG believe this is sufficient to highlight that this group of people need collaborative specialist management.</p>

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SH	British Society of Gastroenterology	3	Full	general		The partners of women with UC who planning a family should be counselling regarding their use of immunosuppressive drugs.	Thank you for your comment. The scope included pregnant women as a group for special consideration. Preconceptual care was beyond the remit of the scope. The planning of pregnancy is mentioned in the clinical introduction to chapter 8.
SH	British Society of Gastroenterology	4	Full	general		<p>The following comments were submitted by the Gastroenterology Department at St Mark's Hospital, Harrow. The BSG wishes to endorse them in their entirety.</p> <p><u>General</u> Severity of ulcerative colitis chart is out of date. CRP > 45 is better than ESR No one convinced about needing 3 dilated small bowel loops to be an indication for surgery (1.1.19). Send stool for C&S, CI difficile and consider biopsy and blood for CMV when relapses. Refer to the IBD MDT which most hospitals have and discusses all complex cases and when surgery may be needed..</p> <p><u>Remission</u> Add comments about the 5ASA dose with which to begin. State high and low 5ASA doses.</p> <p><u>Tacrolimus</u> Tacrolimus is counted as a high cost drug thus can be difficult for Trusts to prescribe without much form filling? Can NICE help</p>	<p>Thank you for your comments.</p> <p>General When discussing measures of disease activity the GDG agreed that the Truelove and Witts' criteria are a useful and widely used measure of disease severity in adults. The GDG acknowledged there are other clinical markers not included in the Truelove and Witts criteria that can be used to measure disease severity.</p> <p>Recommendation 1.1.19 (now 1.2.17) lists the risk factors that may indicate an increased likelihood of needing surgery; their presence should alert clinicians to this possibility. However, the GDG acknowledge that mucosal islands and more than 3 dilated small bowel loops are not part of a validated risk assessment tool and have removed them from the recommendation.</p> <p>The GDG agree that sending stools for C&S, C. difficile and considering biopsy and</p>

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						<p>this?</p> <p>Is tacrolimus a long-term treatment or a bridge to another drug (e.g. azathioprine)?</p> <p>Should patients with severe extensive or left sided disease treated with tacrolimus be changed gradually onto azathioprine/mercaptopurine?</p> <p>Is tacrolimus safe in pregnancy?</p> <p><u>Ciclosporin</u></p> <p>Should ciclosporin be given iv or orally?</p> <p>Where is the place of infliximab? Before or after Ciclosporin?</p> <p><u>Other drugs</u></p> <p>Should in- patients' receive Fragmin prophylaxis?</p> <p>If intolerant of AZA/MP consider methotrexate but what is its effect on both active disease and in being chemopreventative?</p> <p><u>Surveillance</u></p> <p>Give written information to the patients about when they should be referred back to the hospital for surveillance.</p> <p><u>Surgery</u></p> <p>1.2.4 Information about surgery is given by the team (especially the GI surgeon <u>and</u> nurse specialist)</p>	<p>blood for CMV when a person has relapsed is an important part of the management of people with UC. However these areas were not part of the scope as they were not prioritised in the scope consultation or stakeholder workshop. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.</p> <p>We agree that all people with UC should be managed by a multidisciplinary team at all times and this is reflected in recommendation 1.1.1. In addition, recommendation 1.2.10 states that a gastroenterologist and a colorectal surgeon should collaborate to provide treatment and management when a person with acute severe colitis is admitted to hospital, emphasising the importance of different specialities working together.</p> <p>Remission</p> <p>The doses are now included in the recommendation.</p> <p>Tacrolimus</p> <p>The use of tacrolimus has been identified by the NICE Implementation team as a</p>

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							<p>recommendation that will change practice. To facilitate this, the team are considering developing a NICE education resource that explains why these new recommendations are being made and the evidence behind them. The cost impact of implementing the recommendation will also potentially be included in the NICE costing tool.</p> <p>No evidence was identified for the use of tacrolimus in the maintenance of remission. The studies assessing the use of tacrolimus for the induction of remission in people with steroid- refractory ulcerative colitis had a follow up period of 2 weeks (Ogata et al 2006; Ogata et al 2012). As a result the GDG felt unable to make a recommendation on the use of tacrolimus as a long term treatment.</p> <p>No studies were identified on the use of tacrolimus in pregnancy and the GDG were unable to comment on its use in this population group. The scope states that "The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients".</p> <p>Ciclosporin</p>

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							<p>The evidence that supported recommendations 1.2.12 and 1.2.13 (final recommendation numbering) was based on studies that had used IV ciclosporin. For the use of infliximab please refer to TA163 'Infliximab for acute exacerbations of ulcerative colitis'.</p> <p>Other drugs Fragmin The GDG agree this is an important part of the management of in-patients being treated for severe UC. At the stakeholder workshop, it was acknowledged that VTE prophylaxis (fragmin) addressed the complications of ulcerative colitis rather than the disease and was not prioritised for inclusion in the scope. As the use of fragmin for VTE prophylaxis was not reviewed the GDG could not make a recommendation.</p> <p>However NICE 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 VTE in combination with the expectation of ongoing reduced mobility relative to their normal state while in hospital. This has been referred to in section 5.46 (Recommendation and link to evidence;</p>

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							<p>other considerations.</p> <p>Use of methotrexate The GDG comment on the use of methotrexate in the recommendations and link to evidence box on inducing remission (section 5.40; trade off between clinical benefits and harms). There is a 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). 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.</p> <p>Surveillance The GDG agree that people should be given information on surveillance. Recommendation 1.3.7 (now 1.1.3) refers to the NICE clinical guideline 118 'colonoscopic surveillance for colorectal cancer and NICE clinical guideline 27 'referral for suspected cancer '. The other considerations section of the recommendations and link to evidence box on maintaining remission (section 7.25) notes that the GDG recognise the importance of screening for colorectal cancer in people with ulcerative colitis.</p>

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							Surgery We agree it is important that information about surgery is given by members of the multidisciplinary team and feel this is reflected in recommendation 1.1.1, and recommendations 1.3.1 to 1.3.6 (final recommendation numbering).
SH	BSPGHAN	2	Full	15	39	<p>This guideline covers all patients with UC i.e children and adults. It does not seem to emphasize the need for children with IBD to be under the coordinating care of a paediatric gastroenterologist.</p> <p>Without this clear recommendation there is a danger that children are could be managed by adult colorectal surgeons or gastroenterologists in the DGH setting without appropriate consideration to growth or development and without the appropriate knowledge of how IBD differs in children. Children with UC need to be seen at least annually in a tertiary centre by a paediatric gastroenterologist irrespective of the length of apparent remission. In addition they need more regular review (every 3 to 4 months) by a consultant with expertise in gastroenterology or alternatively a paediatric gastroenterologist (depending on the local arrangements).</p> <p>Networks for children with IBD may</p>	<p>Thank you for your comment. The GDG agrees that it is important that young people and children are cared for by an appropriate team.</p> <p>The GDG did not look at specific evidence about the specific composition of the MDT but have highlighted in recommendations 1.1.1 and 1.2.10 'ensure the composition of the multidisciplinary team is appropriate for the age of the person' and recommendation 1.2.10 directly refers to seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person.</p> <p>These recommendations are clear that children should not be managed by adult colorectal surgeons or adult gastroenterologists. However it could be the case in a DGH that a child is under the care of a paediatrician who is advised by a paediatric gastroenterologist.</p> <p>The GDG considered that naming the specific members of the MDT was a service delivery issue and could have significant</p>

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						include an adult gastroenterologist as well as a local Paediatrician with an interest.	<p>impact on resources and were not confident in naming specific specialties.</p> <p>The general follow-up and review of children and young people was not included the scope. The areas covered by the guideline were defined by the scope. These areas were not part of the scope as they were not prioritised in the scope consultation or stakeholder workshop.</p> <p>The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.</p> <p>The monitoring of bone health and growth has been addressed in chapter 9 and recommendations 1.5.2 (now 1.6.2) and 1.5.3 (now 1.6.3) are specific to children and young people.</p>
SH	BSPGHAN	4	Full	Section 4.2 And 4.3	41	These sections are a bit confusing as 4.2 'Key priorities for implementation' simply summarises a lot of the second section, but misses out important bits such as infliximab recommendations. May be better to have the complete part first. Or to introduce the first section more completely so it does very clearly show this is only picking out parts of the whole document	Thank you for your comment. Section 4.2 'Key priorities for implementation' are the recommendations that the GDG has selected as being the recommendations that are most likely to have a high impact on patients' outcomes and on reducing variations in clinical management (in accordance with the NICE Guidelines manual referenced in the introductory paragraph of section 4.2); it is not a simple summary of section 4.3 (which provides the

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							full list of recommendations).
SH	BSPGHAN	5	Full	Section 4.2	41	As the GMC request fully informed documented consent for all off label medicines. This has major implications (probably unrealistic) for paedcs and I do not think has been applied in this way in other NICE guidelines	Thank you for your comment. It is NICE's standard practice, as agreed with the MHRA, to append a footnote to all off-label recommendations in all NICE clinical guidelines.
SH	BSPGHAN	6	Full	Section 1.1.1.0	16	For children and young adults with mild/moderate UC failing to respond to anti-inflammatory therapy a delay of 4 weeks would be rather long before moving to Step 2. Although not evidence based, most practice would likely step up after a maximum of 2 weeks lack of response	Thank you for your comment. We agree with these comments and phrased the recommendation to indicate treatment could be stepped up <i>within</i> 4 weeks. This would allow treatment to be stepped up after a maximum of 2 weeks as suggested.
SH	BSPGHAN	7	Full	Section 1.1.1.1	17	<p>Oral tacrolimus is an uncommon choice for third line therapy in children to induce remission. It is much more likely that early addition of a thiopurine would be encouraged, with prolonged steroid tail to reach thiopurine efficacy,</p> <p>Failing to include biological therapies such as Infliximab directly guideline is already out of date and partly redundant.</p> <p>The use of Infliximab is referenced within the text of this guideline in other NICE guidance e.g. NICE TA 163 (2008). It seems illogical that this has not been "dovetailed" in to this guideline. It would be far simpler if Infliximab were included and there was</p>	<p>Thank you for your comments. The evidence-base for the role of these treatments in the induction of remission is limited in all age groups. The GDG has reflected this absence of evidence in the recommendations and in the 'trade off between clinical benefits and harms' under the heading immunomodulators in the recommendations and link to evidence box (section 5.40).</p> <p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which</p>

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						<p>clarity as to when in the various algorithms e.g. refractory chronic UC or acute severe UC Infliximab can or should be given.</p>	<p>have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA140 review decision (http://guidance.nice.org.uk/TA140/ReviewDecision) noted that the fact that the marketing authorisation for infliximab had been extended to include younger people (aged 6–17 years) and that this fact would be taken into account when NICE scopes its forthcoming multiple technology appraisal of TNF alpha inhibitors.</p>

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							<p>The TA guidance will be presented side by side with the recommendations in the guideline in the NICE Pathway.</p> <p>The cross-reference has been amended to make the relationship of infliximab to ciclosporin clear.</p>
SH	BSPGHAN	8	Full	Section 1.1.1.8	18	Using the well validated PUCAI to assess response to therapy in children with acute severe UC is now a national recommendation from BSPGHAN. The evidence for using the PUCAI is so strong and much better validated than any other score available, is simple and non-invasive and widely used around. We think this is what should be used for our patients	Thank you for your comment. We have included the Paediatric Ulcerative Colitis Activity Index (PUCAI) as the tool to assess the severity of ulcerative colitis in young people and children. In reference to assessing the likelihood of needing surgery the GDG has addressed this issue in the 'other considerations' section of the recommendations and link to evidence box (section 5.53). The GDG noted the PUCAI is used in practice to assess the severity of disease on admission. This index was not included in the review because only one study was identified that compared the PUCAI to other indexes, a derivation study was not identified.
SH	BSPGHAN	9	Full	Section 4.2	6	For children and young people it would be worth specifically mentioning information available from CICRA and NACC	Thank you for your comment. The full guideline contains the methods, evidence and recommendations.
SH	BSPGHAN	10	Full	Section 5	51	Definition of acute severe colitis should be made by paediatric specific tool. As above, the only validated instrument is the PUCAI	Thank you for your comment. We agree and have added in the PUCAI.
SH	BSPGHAN	11	Full	Reco		Recommendation 35 is too vague.	Thank you for your comments.

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				mme ndati on 35		<p>"Consider" should not be used in a recommendation sentence by NICE. The GDG should clearly advocate either the monitoring of bone health with details or not in the specific circumstances described</p> <p>Monitoring growth every 6 or 12 months in children</p>	<p>Recommendation 35</p> <p>The GDG recognised the importance of monitoring bone health however the evidence identified in this area was sparse and of low quality. The GDG note in this in the 'other considerations' section of the Bone health Recommendations and link to evidence box (section 9.7) and how this is reflected in the strength of the recommendation. Please refer to page 8 of the NICE version which explains the strength of NICE recommendations. See also Chapter 9 of the NICE guidelines manual sets out the process for GDGs deciding the strength of recommendations and how they are worded, http://publications.nice.org.uk/the-guidelines-manual-pmg6/developing-and-wording-guideline-recommendations</p> <p>Recommendation 36</p> <p>The timing of monitoring growth was reviewed and no evidence was identified to support the GDG in their decision making. This issue was discussed at length by the GDG. These discussions are summarised in the 'other considerations' section of the Recommendations and link to evidence box of chapter 9. Notably the GDG recognised the difficulties of accurately and reliably</p>

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				Recommendation 36		<p>going through puberty is not sufficient. They need to be seen at least every 4 months in a consultant clinic where their growth is assessed. Maximal growth velocity may only last for 2 years and if you leave it for 12 months before discovering that this is sub-optimal it does not give sufficient time to intervene successfully with either a medical escalation or surgery. This is the time when it is essential that children and young people are being reviewed regularly by expert tertiary paediatric gastroenterologists.</p>	<p>measuring growth and the consequences of measuring growth too frequently (measurement error) but considered the benefits of monitoring growth regularly outweighed any potential risks of infrequent sporadic monitoring. The GDG discussed the optimal frequency of monitoring growth in children and young people and in the absence of evidence considered disease activity to be a reasonable marker for defining frequency. The more severe the disease activity, the use of systemic steroids and during puberty the greater the potential for growth delay. This has been reflected in the recommendation to highlight that monitoring should be done 'every 6 months during pubertal growth if the disease is inactive'.</p> <p>Recommendation 37 (now recommendation 39) The GDG were keen to convey the message that young people and children should have their growth monitored regularly. But as noted in the Recommendations and link to evidence box (section 9.13) there was not any evidence identified on the optimal strategies for monitoring. The GDG considered that naming a location or a specific professional to undertake monitoring would be unhelpful</p>

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				Recommendation 37		<p>This is unrealistic and will not result in effective growth monitoring. Children need to be measured in a standard way, using the correct equipment, in the same setting and by appropriately trained staff. The height and weights then need to be plotted on appropriate centile charts in the case notes and reviewed by the responsible clinician. Senior clinical continuity and coordinating responsibility is essential. Random measurements taken and recorded in different settings will not equate to effective growth monitoring. This point is of crucial importance as commissioners may lose sight of the need for expert, regular tertiary involvement in this potentially vulnerable group.</p>	<p>in implementing this recommendation but have emphasised should be carried out by appropriately trained professionals. Recommendation 39 also now states monitoring should be done as part of the overall clinical assessment, including disease activity, to help inform the need for timely investigation, referral and/or interventions, particularly during critical phase of pubertal growth. The recommendations have been reordered to reflect the measurements should not be done in isolation.</p> <p>Recommendation 41 (now recommendation 38) The GDG agree that children should be under the care of a specialist with appropriate expertise, working as part of a multidisciplinary team. This recommendation does not reflect on the overall general care and who young people and children should be under the care of but specifically to pubertal delay.</p> <p>The recommendations on monitoring of growth and pubertal delay note that monitoring can take place at routine appointments, acute admissions or urgent appointments in primary care, community services or secondary care.</p>

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				Recommendation 41		Children should already be under the care of a tertiary paediatric gastroenterologists with or without shared care with a consultant paediatrician with a special interest / post graduate expertise in the care of paediatric IBD. This does not seem implicit in this recommendation.	The aim of this recommendation is to ensure that young people with delayed pubertal development have a timely referral to someone either with the access to or the expertise to investigate pubertal delay.
SH	Crohn's and Colitis UK	1	Full	14	29	Current medical approaches include improving quality of life – we would like to see a recognition of patient defined outcomes such as the ability to maintain employment or education recognised as a treatment goal	Thank you for your comment. The GDG agree that these are important outcomes. While these outcomes were not specifically identified, quality of life was identified as a critical outcome for every review where appropriate. Quality of life was seen as a composite measure that reflected these factors. The review protocols list the GDG

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							selected outcomes (see Appendix C).
SH	Crohn's and Colitis UK	2	Full	General		<p>As commissioning groups seek to provide more care in the community, Crohn's and Colitis UK would like to highlight the following issues for patients who are no longer under review in secondary care: There is an increased risk of colorectal cancer for UC patients, particularly those who have had extensive ulcerative colitis for more than 8 years. For this reason these patients should be placed in a cancer surveillance programme. Having extensive disease does not always correlate with active symptoms that would make the patient seek medical help. It is possible for patients to have extensive but quiescent disease which places them at higher risk of colorectal cancer, and for those patients who are not under the care of a specialist team it is likely they will not be placed into cancer surveillance.</p> <p>It is common for patients with long-term conditions to normalise and tolerate a certain level of symptoms and this may lead to a gradual deterioration in their quality of life which they do not perceive as a change warranting medical attention. Patients with long-standing disease may also have a very out-of-date understanding of what treatment can offer. In the case of IBD their previous</p>	<p>Thank you for your comment. The GDG agree that people should be given information on surveillance. Recommendation 1.3.7 (now 1.1.3) refers to the NICE clinical guideline 118 'colonoscopic surveillance for colorectal cancer and NICE clinical guideline 27 'referral for suspected cancer'. The other considerations section of the recommendations and link to evidence box on maintaining remission (section 7.25) notes that the GDG recognise the importance of screening for colorectal cancer in people with ulcerative colitis.</p> <p>These guidelines are intended as guidance for clinicians in all settings and will support GPs in their understanding of best practice in treatments for people with UC.</p> <p>The timing of follow up and the review of people with ulcerative colitis was not part of the scope. These areas were not part of the scope as they were not prioritised in the scope consultation or stakeholder workshop. As these topics were not reviewed, the GDG could not make a recommendation on them. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a</p>

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						<p>experiences may have been limited to corticosteroids from which they may have experienced significant adverse effects. One of the main areas of improvement in IBD care has been more targeted therapy with a reduction in systemic side effects. Clinicians also now use immunosuppressive drugs much more readily and these can provide a level of symptom control that patients are not aware can be achieved.</p> <p>Most GP practices have very few IBD patients and therefore are unlikely to develop an expertise in management. Indeed there is a real risk that their understanding of best practice will be out-of-date. This has been illustrated in two recent unpublished studies looking at the ongoing medical management of patients not under the care of IBD specialists. A significant number of patients were being under-treated.</p> <p>It should be a responsibility of GP practices (and of commissioners of healthcare) to ensure that these patients have an annual review and are referred for specialist care if required. There should be a local Register of all IBD patients to facilitate this annual review process as set out in the IBD Standards.</p>	workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.
SH	Crohn's and	3	Full	42	16	Patients should have access to a parallel	Thank you for your comment. We agree that

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	Colitis UK				- 20	or joint surgical-medical clinic in a unit that meets the standards set out in the Quality Care Service Standards (The IBD Standards Group)	people with ulcerative colitis should be managed within a multidisciplinary team and this is stated in recommendation 1.1.1. Access to specific clinics was not included in the scope. This area was not part of the scope as it was not prioritised in the scope consultation or stakeholder workshop. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.
SH	Crohn's and Colitis UK	4	Full	42	18	Information should include possible impact on fertility or sexual function	Thank you for your comment. Pages 41-42 of the full guideline provide the 'key priorities for implementation'. Please refer to the full list of recommendations provided in section 4.3; recommendation 23 (now 24) second bullet point addresses the point on information about sexual function. We cannot comment on fertility as this is outside of the scope. Fertility was not included in the scope. This area was not part of the scope as it was not prioritised in the scope consultation or stakeholder workshop. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder

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							consultation in June–July 2011, after which the scope was amended. Please refer to recommendation 1 about giving information.
SH	Crohn's and Colitis UK	5	Full	42	21 - 27	This information should be part of pre-operative counselling. Patients being considered for surgery should be offered the option of talking to patients who have had pouch surgery or a permanent stoma.	Thank you for your comment. The recommendation stresses the importance of info from the stoma nurse and IBD nurse specialist, colorectal surgeon. The option of discussion with other patients is covered in the Recommendations and link to evidence box (section 6.6).
SH	Crohn's and Colitis UK	6	Full	General		Information should include contact details for the relevant patient organisations	Thank you for your comment. The full guideline contains the methods, evidence and recommendations.
SH	Crohn's and Colitis UK	7	Full	General		The absence of recognition of the ileal pouch register, introduced to raise standards in pouch surgery, is regrettable	Thank you for your comment. Surgical techniques and their outcomes were not part of the scope. These areas were not part of the scope as they were not prioritised in the scope consultation or stakeholder workshop. As these topics were not reviewed, the GDG could not make a recommendation on them. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.
SH	Crohn's and Colitis UK	8	Full	178	26	We welcome the recognition of the importance of access to psychologists and	Thank you for your comment. Access to psychologists and counsellors was not

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						counsellors, but suggest a need for further research and would support this as a research recommendation	within the remit of this guideline and therefore the GDG was unable to comment on future research in this area.
SH	Department of Health	1	Full	1	General	The Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
SH	Dr Falk Pharma UK Ltd	1	Full	39		The algorithm should be more explicit on the need to optimise aminosalicylate therapy before progressing to steroids. Variables such as dose, formulation and release characteristics as well as patient choice should be optimised before turning to steroids.	<p>Thank you for your comment.</p> <p>The evidence reviews for the induction of remission included variables that addressed the issue of optimisation of aminosalicylate therapy (dose, formulation, regime, mode of delivery and interclass comparisons where possible). When reviewing the evidence and balancing the benefits and harms of a treatment the GDG did not find any compelling evidence that indicated there was another choice of treatment before steroids.</p> <p>This was supported by the economic model. The rationale is summarised throughout the Recommendations and link to evidence box (section 5.40).</p> <p>The dose recommended is already a high dose and no clinical differences were found between formulations or release characteristics. Patient choice is highlighted in recommendations 1.2.1 to 1.2.6 (final recommendation numbering) on induction therapy.</p>
SH	Dr Falk Pharma UK Ltd	2	Full	39		There should be mention of steps to take for 1 st time non-responders and if there is	Thank you for your comment. Treatment for first time non-responders and for people

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						continued non-response – optimisation of therapy.	with continued non-response is detailed in Step 2 of the algorithm.
SH	Dr Falk Pharma UK Ltd	3	Full	39		There should be a direct link (a horizontal arrow) between the first and second boxes for step 1 therapy.	Thank you for your comment. The boxes are separate as these are referring to treatments for different populations.
SH	Dr Falk Pharma UK Ltd	4	Full	39		There should be greater clarity on use of prednisolone and budesonide rectal preparations.	Thank you for your comment. Recommendation 1.2.2 outlines the use of rectal corticosteroids for 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. The GDG were unable to comment on the use of any particular preparation due to the paucity of evidence for any preparation. Further details of the reviews and the rationale for the recommendations are provided in chapter 5 (section 5.8 and 5.40) on the induction of remission.
SH	Dr Falk Pharma UK Ltd	5	Full	41	1	A discussion on topical steroids needs to be added.	Thank you for your comment. Section 4.2 'Key priorities for implementation' are the recommendations that the GDG has selected as being the recommendations that are most likely to have a high impact on patients' outcomes and on reducing variations in clinical management (in accordance with the NICE Guidelines manual referenced in the introductory paragraph of section 4.2); it is not a simple summary of section 4.3 (which provides the full list of recommendations).

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							There is no evidence for the use of topical steroids as a treatment step after topical aminosalicylates for people with distal disease who are resistant to the aminosalicylates. 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 context.
SH	Dr Falk Pharma UK Ltd	6	Full	42	29	There is no evidence that side effects increase with once daily dosing. The statement that once-daily dosing may lead to more side effects should be removed.	Thank you for your comment. The review and meta- analysis shows that there are more adverse events (RR 1.12, 95% CI 1-1.26) and serious adverse events (RR 1.61, 95% CI 1.03-2.53) with once-daily dosing (see table 93). The GDG considered these effects to be clinically important.
SH	Dr Falk Pharma UK Ltd	7	Full	43	22	A step for topical steroids is needed	Thank you for your comment. There is no evidence for the use of topical steroids as a treatment step after topical aminosalicylates for people with distal disease who are resistant to the aminosalicylates. 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 context.
SH	Dr Falk Pharma UK Ltd	8	Full	44	15	A step for topical steroids is needed	Thank you for your comment. There is no evidence to support the use of topical steroids in the left sided and extensive

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							population. The GDG agreed this would be an inappropriate treatment for this population due to the limitations of a topical steroid in reaching the affected areas of the bowel.
SH	Ferring Pharmaceuticals		Full	48	29	We feel that it should be clarified that not all mesalazines are licenced for once daily use in maintenance of remission of ulcerative colitis and that responsibility for their use would therefore lie with the clinician. Asacol (all oral formulations), Octasa 400mg, Salofalk 1.5 mg (which these NICE guidelines classify as "low dose") and Mesren do not have a once daily licence. Mezavant, Pentasa and Octasa 800mg do. High doses of Salofalk of 3mg are licenced for once daily administration in patients at increased risk of relapse. Dosing taken from product SPCs at www.medicines.org.uk	Thank you for your comment. A footnote has been added to note that not all the mesalazines are licensed for once daily use.
SH	Ferring Pharmaceuticals	1	Full	41	22	We would suggest a stronger recommendation for combination therapy in light of; the strong evidence for the effectiveness of combined oral and topical therapy, as well as an acceptance by patients for enema administration in an induction context (Vecchi et al 2001 and Marteau et al 2005). Additional benefit for combination therapy was also demonstrated in a cost analysis which showed combined oral and topical mesalazine was more cost effective than	Thank you for your comment. The wording of recommendations reflects the quality of the evidence underpinning them. Chapter 9 of the NICE guidelines manual sets out the process for GDGs deciding the strength of recommendations and how they are worded. See http://publications.nice.org.uk/the-guidelines-manual-pmg6/developing-and-wording-guideline-recommendations The GDG were not confident that the

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						oral mesalazine administration alone (Connolly 2009).	evidence for combination therapy was strong enough to warrant a 'use' recommendation. This is further explained in 'Trade off between clinical benefits and harms' section of the induction Recommendations and link to evidence box (section 5.40).
SH	Ferring Pharmaceuticals	2	Full	42	30	Evidence of increased side effects with once daily dosing has not been shown for all mesalazines. The PODIUM study by Dignass et al (2009), showed no significant difference in the overall incidence of adverse events between the once daily and twice daily treatment groups (49.2% once daily vs 36.4% twice daily; P=0.24). Furthermore it showed that there was no difference in the types of adverse events between the two groups.	Thank you for your comment. The review and meta- analysis shows that there are more adverse events (RR 1.12, 95% CI 1-1.26) and serious adverse events (RR 1.61, 95% CI 1.03-2.53) and with once- daily dosing (see table 93). The PODIUM study by Dignass et al (2009) was included in both meta analyses.
SH	Ferring Pharmaceuticals	3	Full	44	19	As for page 41, line 22. Given the strong evidence of the effectiveness of combined oral and topical therapy and patients acceptance of enemas in an induction context (Vecchi et al 2001 and Marteau et al 2005), and for oral and topical mesalazine being more cost effective than oral mesalazine alone (Connolly 2009) and the cost analysis; we would suggest a stronger recommendation for combination therapy. We would highlight that topical therapy should be given, unless following discussion with the patient, where it is explained that oral	Thank you for your comment. The wording of recommendations reflects the quality of the evidence underpinning them. Chapter 9 of the NICE guidelines manual sets out the process for GDGs deciding the strength of recommendations and how they are worded. See http://publications.nice.org.uk/the-guidelines-manual-pmg6/developing-and-wording-guideline-recommendations The GDG were not confident that the evidence for combination therapy was strong enough to warrant a 'use'




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						mesalazine alone may not be as effective as combined therapy, the patient indicates a preference against.	recommendation. This is further explained in 'Trade off between clinical benefits and harms' section of the induction Recommendations and link to evidence box (section 5.40).
SH	Ferring Pharmaceuticals	4	Full	48	2	We would highlight the importance of once daily dosing when selecting a mesalazine for maintenance treatment. This would be consistent with the statement in the "All extents of disease" section which follows it (Page 48 Line 10 -13), tying in with the impact of once daily dosing on patient adherence.	Thank you for your comment. This is already covered by the recommendation in the 'all extents of disease' section.
SH	Ferring Pharmaceuticals	5	Full	48	12	As described for page 42 line 30; evidence of increased side effects with once daily dosing has not been shown for all mesalazines. The PODIUM study by Dignass et al (2009), showed no significant difference in the overall incidence of adverse events between the once daily and twice daily treatment groups (49.2% once daily vs 36.4% twice daily; P=0.24). Furthermore it showed that there was no difference in the types of adverse events between the two groups.	Thank you for your comment. The review and meta- analyses (that included the PODIUM study) shows that there are more adverse events (RR 1.12, 95% CI 1-1.26) and serious adverse events (RR 1.61, 95% CI 1.03-2.53) with once-daily dosing (see table 93). The GDG considered these effects to be clinically important.
SH	Ferring Pharmaceuticals	6	Full	52	28	We suggest that 5-ASA and corticosteroids are reversed in the sentence as 5-ASAs are the more widely used drugs in this instance and that the order matches that in which 5-ASAs and corticosteroids are used. We would also highlight that the	Thank you for your comment. The GDG are happy with the order of 5-ASA and corticosteroids in the sentence. The sentence with 'loss of integrity' begins with 'depending on the preparation'. The sentence is clear that it is referring to two examples of release mechanisms in the 5-

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						mesalazine in Pentasa is not released by a loss of integrity of it's coating. It is released at all enteral pH conditions by sustained diffusion through a semi permeable membrane, ensuring sufficient 5-ASA is available throughout the gut.	ASAs.
SH	Ferring Pharmaceuticals	7	Full	87	17	<p>We would submit that the Pentasa 4g/day for induction of remission in PINCE (Marteau et al 2005) is also effective in patients. The authors of the review being summarised (Feagan et al 2012 – Induction of remission) do include the 2g/day and 4g/day doses;</p> <p><i>“Among patients with mildly active ulcerative colitis a dosage of 4g/day to 4.8 g/day does not appear to provide any additional benefit over a dosage of 2g/day to 2.4 g/day. Patients with severe symptoms and moderately active disease may benefit from an initial dosage of 4 to 4.8 g/day.”</i></p> <p>We feel that this dose range should be included to give the full picture and to not exclude Pentasa's licenced induction dose.</p>	Thank you for your comment. This refers to the conclusion summarised from Feagan et al 2012 and it would be inappropriate to change their conclusion by including the 2g and 4g dose in the text.
SH	Ferring Pharmaceuticals	8	Full	108	3	Please find attached to the email an abstract of a cost analysis by Connolly et al 2013 comparing the economics of 4g mesalazine once daily with 2g twice daily.	Thank you for your comment. We do not routinely include abstracts in the economic reviews as stated in the methods chapter (3) of the guideline.

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						  Connolly ECCO 2013 Connolly 2013 4g OD HE Abstract.pdf vs 2gBD cost analysis	
SH	Ferring Pharmaceuticals	9	Full	114	11	<p>In early March the MOTUS study investigating once daily dosing of mesalazine 4g compared to 2g twice daily for induction of remission of acute ulcerative colitis (Flourie et al 2013) is due to be published in full in the Alimentary Pharmacology Therapeutics.</p>  MOTUS Flourie et al 2013.pdf	Thank you for letting us know about this study that is due to be published. All searches were updated on 15 th November 2012. No papers published after this date were considered for inclusion in the reviews.
SH	Ferring Pharmaceuticals	10	Full	213	24	<p>We would like to highlight that Ito 2010 study used 2.25 g/day of Pentasa and not 2.4g/day. The formulation of Pentasa used in this study is not used in the UK. While we appreciate other Pentasa and Asacol studies are not comparable, given that Ito 2010 was performed in a Japanese population and therefore of limited relevance to the UK, we would draw your attention to the difference in remission rates between the ASCEND and PODIUM studies. In particular the abstract by Katz, S. et al 2007 which applied UCDAI scoring stringency to the ASCEND studies remission rates. PODIUM and the</p>	<p>Thank you for your comment. The dose in the text has been changed to clarify this. The GDG agreed that 2.25g could be considered close enough to 2.4g to be included in the analysis and it was reasonable to include the ITO study even though the population was Japanese. The GDG did not consider that that these factors would impact on the relevance of these results to a UK population.</p> <p>Thank you for your comments on the ASCEND and PODIUM studies. The ASCEND studies are reviewed in the induction of remission chapter and the</p>

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						ASCEND studies are not directly comparable even looking at the Katz figures but we feel looking at this as a perspective provides balance to the inclusion of the Ito 2010 study.	PODIUM study in the maintenance of remission chapter and we agree are not directly comparable.
SH	Ferring Pharmaceuticals	11	Full	213	31	We would highlight that the PODIUM study (Dignass, A. et al 2009) demonstrated significantly improved remission rates with once daily compared to twice daily dosing.	Thank you for your comment. We agree it is a significant improvement however the evidence statements summarise the clinical importance which is based on the GDG judgement using the absolute difference (refer to methods chapter section 3.3.8).
SH	Ferring Pharmaceuticals	12	Full	221	12	We would question the inclusion of the Yen et al (2008) study, a US study, which uses assumptions made on similarities with Crohn's disease. Certainly we feel the limitations of the study should be made clear to the reader of the guidelines.	Thank you for your comment. The Yen et al (2008) study was included to highlight the published evidence available for this topic. The limitations were noted in the Appendix G however this has been made clearer in the full guideline. An original economic analysis was conducted using UC specific inputs.
SH	MSD Ltd	1	Full	General		<p>Although this clinical guideline covers children, adolescents, and adults, MSD feels that it would be beneficial to provide more specific information regarding treatment in children and adolescents, particularly as fewer therapeutic options are available to this group of patients</p> <p>The role of infliximab as the only licensed biologic therapy in children and adolescents should be clearly acknowledged, particularly as it is even</p>	<p>Thank you for your comment. The GDG recognised the importance of providing information specific to children and young people and have reflected this in the recommendations where the evidence allowed this distinction.</p> <p>Please refer to recommendations 1.2.5, 1.2.10 and 1.4.3 (final recommendation numbering) where the recommendations are specific to treatments for children and young people.</p> <p>The GDG noted the paucity of evidence for</p>

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						<p>more desirable for children and adolescents to have access to effective treatments that delay or prevent surgery - which can have long-term consequences; 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)</p>	<p>treatments for young people and children.</p> <p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process. TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side by side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	2	Full	General		MSD feels that the patient populations presented in this clinical guideline and the	Thank you for your comment. There was extensive discussion by the GDG on the

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						<p>language used to define these populations does not accurately reflect the perspective of clinicians, particularly the description given in NICE TA140 (briefly referenced by this clinical guideline) of “sub-acute” patients. MSD kindly suggests that referring to these patients as having moderately to severely active ulcerative colitis is more reflective of clinician perspectives than the term “sub-acute”</p> <p>It is important for this clinical guideline to consider and provide recommendations for patients with moderately to severely active ulcerative colitis. Therefore, MSD encourages the inclusion of recommendations for patients with moderately to severely active ulcerative colitis (currently described as "sub-acute" patients)</p> <p>As reference, please note that:</p> <p>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</p>	<p>terminology used clinically for people who have symptoms that are at the top range of moderate disease but can be managed in an outpatient setting. In this guideline the term ‘subacute’ was chosen to describe this population and the definition is based on that used in NICE TA140 ‘Infliximab for subacute manifestations of ulcerative colitis’.</p> <p>This decision was based on: the GDG’s belief that this is a term understood by clinicians; to maintain consistency across NICE guidance; and in the absence of any other consistent term in the literature. The GDG also noted if this population was referred to as having ‘moderately to severely active ulcerative colitis’ without further explanation and in the place of subacute then people with severely active ulcerative colitis could be treated inappropriately.</p> <p>The GDG agree it is important that the needs of patients who have symptoms that are at the severe end of the moderate disease category are considered in this guideline. Recommendations 1.1.5 (now 1.2.3), 1.1.8 (now 1.2.6) and 1.1.9 (now 1.2.9) refer to treatment for the subacute population.</p>

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						<p>Infliximab now has 5 years of licensed experience in ulcerative colitis having gained its license in March 2006</p> <p>In addition, MSD would note that the pivotal clinical trials and the majority of data on the use of infliximab in ulcerative colitis are for the moderately to severely active patient population</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors.</p> <p>Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side by side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	3	Full	General		Throughout this guideline, biologic therapies such as infliximab are not	Thank you for your comment. Infliximab has been reviewed in NICE technology

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						<p>adequately referred to within the recommendations for treatment, despite infliximab being indicated for the treatment of moderately to severely active ulcerative colitis and recommended for use in acute severe ulcerative colitis by NICE TA163</p> <p>MSD is concerned that through omitting information relating to infliximab, this clinical guideline will not be properly reflective of current clinical practice where clinicians are utilising infliximab in accordance with existing NICE guidance</p>	<p>appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process.</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA guidance will be presented side by side with the recommendations in the guideline in the NICE Pathway.</p> <p>The cross-reference has been amended to make the relationship of infliximab to ciclosporin clear.</p>

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SH	MSD Ltd	4	Full	General		MSD is concerned that the clinical guideline will be out-of-date when finalised, and may not adequately reflect the increasing emphasis on early treatment, the prospect of patients rapidly moving through different treatments, and the growing emphasis on surgery as a last resort as opposed to a cure	Thank you for your comment. We have used the most current evidence available for an evidence-based guideline.
SH	MSD Ltd	5	Full	14	37-43	<p>MSD welcomes the inclusion of the results of the third national IBD audit and believes that the observations made by the IBD audit are of critical importance</p> <p>The IBD audit demonstrates that there is relatively low uptake of anti-TNFs in patients who have not responded to corticosteroids (16.8%), despite the ability of anti-TNFs to successfully elicit a response in a high proportion of these patients, more effectively than ciclosporin (85% response with infliximab compared to 64% with ciclosporin treatment)</p> <p>These data would suggest a need to change clinical practice by increasing the uptake of anti-TNFs, thus providing an effective means of obtaining a response in patients for whom intravenous steroids have proven ineffective</p>	Thank you for your comment.

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SH	MSD Ltd	6	Full	14	44	The clinical guideline states that “most patients receive maintenance treatment with aminosalicylates”. MSD kindly suggests that the role of infliximab as an option for the maintenance of remission should be acknowledged	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 ‘Infliximab for subacute manifestations of ulcerative colitis’ and TA163 ‘Infliximab for acute exacerbations of ulcerative colitis’ which have been cross referred to in the guideline.</p> <p>The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012.</p> <p>It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p>
SH	MSD Ltd	7	Full	17	37	MSD is concerned that the stated remit (“to produce a clinical guideline on the management of ulcerative colitis”) has not	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 ‘Infliximab for

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						<p>been fully addressed in this draft version</p> <p>MSD notes the limited presentation of data and recommendations relating to the use of infliximab within the management of ulcerative colitis despite infliximab being indicated for the treatment of moderately to severely active ulcerative colitis and recommended for use in acute severe ulcerative colitis by NICE TA163</p> <p>MSD is disappointed to note that our previous comments relating to the inclusion of infliximab in the draft scope and its subsequent omission from the final scope have not been addressed in order to include infliximab within this draft clinical guideline</p>	<p>subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	8	Full	18	28-33	In the bulleted list of drug categories covered within this clinical guideline, anti-TNFs have been omitted, despite infliximab being indicated for the treatment of moderately to severely active ulcerative	Thank you for your comment. Infliximab has been reviewed in TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which

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						<p>colitis and recommended for use in acute severe ulcerative colitis by NICE TA163</p> <p>MSD is disappointed to note that our previous comments relating to the inclusion of infliximab in the draft scope and its subsequent omission from the final scope have not been addressed in order to include infliximab within this draft clinical guideline</p>	<p>have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process.</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal, including other tumour necrosis factor (TNF) alpha inhibitors, including the terminated appraisal 'Adalimumab for the treatment of moderate to severe ulcerative colitis (TA262). NICE will also request a referral for an appraisal of golimumab for ulcerative colitis to be included in this multiple technology appraisal. See http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side by side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	9	Full	21		In the third row and third column of the table describing review questions, the following review question omits infliximab	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for

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						<p>from consideration: "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?"</p> <p>MSD feels that the review question should be expanded to include infliximab, thereby ensuring that this clinical guideline is an accurate reflection of current clinical practice - which includes infliximab use for patients with acute severe ulcerative colitis as recommended by NICE TA163</p>	<p>subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	10	Full	21		<p>In the fourth row and third column of the table describing review questions, the following review question omits infliximab from consideration: "In adults, children and young people with ulcerative colitis in remission, what is the clinical and cost-</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which</p>

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						<p>effectiveness of corticosteroids, aminosaliclates, immunomodulators (mercaptopurine, azathioprine, methotrexate and tacrolimus) for the maintenance of remission compared to themselves (different preparations and doses), each other, combinations of preparation (oral and topical) and placebo?"</p> <p>MSD feels that the review question should be expanded to include infliximab, thus acknowledging the role of infliximab in the maintenance of remission</p>	<p>have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process.</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedialive/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	11	Full	39		The reproduction of the image is poor, the clarity of the figure should be improved	Thank you for your comment. Unfortunately resolution of the algorithms is lost slightly when embedding them into the full guideline. However, to address this issue we will publish the algorithms separately for better clarity as a stand-alone PDF file (resolution is retained) on the NICE website.
SH	MSD Ltd	12	Full	40		The reproduction of the image is poor, the	Thank you for your comment. Unfortunately

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						clarity of the figure should be improved	resolution of the algorithms is lost slightly when embedding them into the full guideline. However, to address this issue we will publish the algorithms separately for better clarity as a stand-alone PDF file (resolution is retained) on the NICE website.
SH	MSD Ltd	13	Full	39 -40		<p>The two treatment algorithms presented within this clinical guideline cover mild to moderate ulcerative colitis and acute severe ulcerative colitis</p> <p>MSD believes that the coverage provided by these two algorithms is inadequate as neither includes patients with moderately to severely active ulcerative colitis, i.e. those patients not requiring hospitalisation but still experiencing considerable clinical, quality of life, and productivity burdens as a result of their disease</p> <p>MSD kindly suggests that this clinical guideline should provide information to guide clinical practice for the treatment of patients with moderately to severely active ulcerative colitis</p>	<p>Thank you for your comment. Treatment for patients with moderately to severely active ulcerative colitis (defined in this guideline as people with subacute ulcerative colitis) is outlined in Algorithm 1 under Step 1 therapy in boxes 3 and 6.</p> <p>There was extensive discussion by the GDG on the terminology used clinically for people who have symptoms that are at the top range of moderate disease but can be managed in an outpatient setting. In this guideline the term 'subacute' was chosen to describe this population and the definition is based on that used in NICE TA140 'Infliximab for subacute manifestations of ulcerative colitis'.</p>
SH	MSD Ltd	14	Full	40		Infliximab is referred to in an isolated box within the treatment algorithm that states "Refer to NICE technology appraisal guidance 163 for guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease)."	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline.

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						<p>MSD believes that this box and the text contained within are not sufficient to clearly indicate the place of infliximab within the treatment algorithm</p> <p>MSD proposes that a box for infliximab should be added at the same level as ciclosporin, to demonstrate that in cases where ciclosporin is contraindicated or is considered to be inappropriate, infliximab should be considered as another treatment option</p> <p>It could be further argued that both ciclosporin and infliximab should be considered at an earlier point within the treatment algorithm than surgery (i.e. not on the same level). This would then reflect the availability of treatment options that delay or prevent surgery, which can be associated with negative long-term consequences for patients (Sager PM. IBD. 2003; 491-511)</p>	<p>Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process.</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors.</p> <p>Refer to http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p>
SH	MSD Ltd	15	Full	42	1 -5	For the induction of remission the addition of ciclosporin to intravenous corticosteroids or surgery have been considered. However, infliximab has been recommended by NICE in the acute severe population (NICE TA163), and therefore, al college MSD kindly suggests that infliximab should also be considered	Thank you for your comment. Section 4.2 'Key priorities for implementation' are the recommendations that the GDG has selected as being the recommendations that are most likely to have a high impact on patients' outcomes and on reducing variations in clinical management (in accordance with the NICE Guidelines manual referenced in the introductory

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							paragraph of section 4.2). The GDG did not prioritise TA163 'Infliximab for acute exacerbations of ulcerative colitis' as a key priority for implementation compared to the other recommendations listed.
SH	MSD Ltd	16	Full	42	28 -31	MSD kindly suggests that the role of infliximab as an option for the maintenance of remission should be acknowledged	<p>Thank you for your comment. The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedialive/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012.</p> <p>It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p>
SH	MSD Ltd	17	Full	43	7 -11	NICE TA140 states that "sub-acute" patients are defined as having "moderately to severely active ulcerative colitis that would normally be managed in an outpatient setting and does not require	Thank you for your comment. The GDG agree it is important that the needs of patients who have symptoms that are at the severe end of the moderate disease category are considered in this guideline.

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						<p>hospitalisation or the consideration of urgent surgical intervention”</p> <p>This definition is briefly referenced in this clinical guideline. However, MSD notes that no actual guidance is provided within this draft version for the management of patients with moderately to severely active disease, despite the availability of treatments such as infliximab (which have an indication for moderately to severely active ulcerative colitis)</p> <p>As reference, please note that:</p> <p>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</p> <p>Infliximab now has 5 years of licensed experience in ulcerative colitis having gained its license in March 2006</p> <p>In addition, MSD would note that the pivotal clinical trials and the majority of data on the use of infliximab in ulcerative</p>	<p>Recommendations 1.1.5 (now 1.2.3), 1.1.8 (now 1.2.6) and 1.1.9 (now 1.2.9) refer to treatment for the subacute population.</p> <p>Infliximab has been reviewed in NICE technology appraisal guidance TA140 ‘Infliximab for subacute manifestations of ulcerative colitis’ and TA163 ‘Infliximab for acute exacerbations of ulcerative colitis’ which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 ‘Infliximab for subacute manifestations of ulcerative colitis’ will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p>

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						colitis are for the moderately to severely active patient population	The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.
SH	MSD Ltd	18	Full	43	7 -8	At this, and at all subsequent references to NICE TA140 throughout the document, MSD feels that it would be beneficial to indicate that this appraisal will be under review in the forthcoming MTA for ulcerative colitis	Thank you for your comment. Infliximab has been reviewed in TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Readers who refer to TA140 'Infliximab for subacute manifestations of ulcerative colitis' can follow the progress of the forthcoming proposed MTA.
SH	MSD Ltd	19	Full	45 -46	20 -35	<p>Within the section "treating acute severe ulcerative colitis: all extents of disease" (through to page 46, line 7), MSD feels that the role of infliximab should be stated more clearly, rather than solely referring users to the separate NICE TA163 document</p> <p>MSD kindly suggests that additional wording is included to explain the role of infliximab more clearly, for instance, through acknowledging that infliximab provides an additional option for treatment in line with its indication (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</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be</p>

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						(AZA), or who are intolerant to or have medical contraindications for such therapies)	<p>updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	20	Full	45	17-19	The data supporting the guidance around tacrolimus for the induction of remission relate to two small trials where N=101 and N=41 (referenced on page 151, line 2). These trials were appraised to be of "very low quality" evidence and indicated that there was no clinically important difference between tacrolimus and placebo for the induction of remission, and as such MSD feels that the guidance for its use is unwarranted, particularly as tacrolimus does not have an indication for this usage	<p>Thank you for your comment. Thank you for your comment.</p> <p>The GDG recognise that the evidence for all the immunomodulators reviewed is limited and of very low quality. This made any decision on the use of immunomodulators difficult. However the GDG considered it was important to have a treatment option for patients that are refractory to systemic steroids. The GDG decided to recommend tacrolimus over the use of other immunomodulators for the following reasons; the lack of evidence to support the use of methotrexate, the GDG felt azathioprine takes too long to have an effect and its role is limited for induction of remission and in people who have not responded to prednisolone, and</p>

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							the GDG noted benefit of tacrolimus (Ogata et al 2006; Ogata 2012). The GDG acknowledged that nephrotoxicity and opportunistic infections may be an issue with longer term use of tacrolimus and recommended regular monitoring/. This is reported in the 'trade of between clinical benefits and harms' section of the induction.
SH	MSD Ltd	21	Full	48	18 -19	Regarding point 31 - MSD feels that the role of infliximab as an option for the maintenance of remission should be acknowledged, particularly as patients can become refractory to azathioprine, and therefore require alternative treatments	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline.</p> <p>The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012.</p> <p>It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in</p>

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							<p>induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	22	Full	50	2 -6	The first and second research recommendations refer to moderate populations which is inconsistent with the language used in the rest of the clinical guideline (where mild to moderate disease is considered, but not moderate alone)	Thank you for your comment. The paucity in the evidence is in the moderate disease population where you would be considering the choice between ASA and prednisolone. Prednisolone would be less likely to be a treatment option with mild disease. Please refer to Appendix M which provides the GDG's rationale for formulating the research recommendations.
SH	MSD Ltd	23	Full	50	7 -9	<p>The third key research recommendation questions the benefits, risks, and cost-effectiveness of methotrexate, ciclosporin, tacrolimus, and infliximab</p> <p>Given that clinical and cost-effectiveness evidence is already available for infliximab, MSD kindly suggests that this evidence be included within this clinical guideline</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in</p>

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							<p>the technology appraisal process. TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedialive/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	24	Full	52	26 -34	In the paragraph describing pharmacological treatments for ulcerative colitis, anti-TNFs have been omitted, despite infliximab being indicated for the treatment of moderately to severely active ulcerative colitis and recommended for use in acute severe ulcerative colitis by NICE TA163	Thank you for your comment. NICE TA163 'Infliximab for acute exacerbations of ulcerative colitis' is referred to in the last paragraph of section 5.1 indicating its use for people with acute severe ulcerative colitis.
SH	MSD Ltd	25	Full	160	2 -6	MSD feels that the review question should be expanded to include infliximab, thereby ensuring that this clinical guideline is a more accurate reflection of clinical practice - which includes infliximab use for patients with acute severe ulcerative colitis as recommended by NICE TA163	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.

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							<p>Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors.</p> <p>Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	26	Full	167		<p>Within the yellow boxed section "Treating acute severe ulcerative colitis: all extents of disease" (through to page 168), the role of infliximab should be stated more clearly, rather than solely referring users to the separate NICE TA163 document</p> <p>MSD kindly suggests that additional wording is included to explain the role of infliximab more clearly, for instance,</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline.</p> <p>Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Updating the TAs was not part of the remit</p>

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						through acknowledging that infliximab provides an additional treatment option in line with its indication (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)	<p>of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedialive/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	27	Full	169		In the grey boxed section "Other considerations", it is stated that GETAID CYSIF study is due to report in 2011. This study has already reported and data were presented at ECCO in February 2011 and again at DDW in May 2011. Essentially CYSIF demonstrated that infliximab and ciclosporin had similar efficacy at Day 7 (infliximab 86% vs. ciclosporin 84% remission), although the ciclosporin group	<p>Thank you for your comment. We have amended the text to report that the GETAID CYSIF study has been reported and the CONSTRUCT study will be reported in 2015 and both are awaiting publication.</p> <p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for</p>

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						<p>suffered significantly more side effects. MSD kindly suggests that these data should be included within this clinical guideline to ensure that it is not an out-of-date resource</p> <p>In addition, the CONSTRUCT study, which was stated to be reporting in 2012, has not yet reported and as such the expected reporting date should be updated</p>	<p>subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	28	Full	181		In the yellow boxed section "Information when considering surgery", MSD feels that it is important to acknowledge the benefits to patients in using infliximab for the	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis'

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						induction of remission (with remission normally achieved within 14 weeks of initiating treatment), therefore delaying or preventing the need to elect surgery - which can be associated with negative long-term consequences for patients (Sager PM. IBD. 2003; 491-511)	and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012 The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.
SH	MSD Ltd	29	Full	185	9 -10	For the maintenance of remission aminosalicylates and immunomodulators have been considered. MSD kindly suggests that the role of infliximab as an option for the maintenance of remission	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute

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						should be acknowledged	<p>exacerbations of ulcerative colitis' which have been cross referred to in the guideline.</p> <p>The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012.</p> <p>It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	30	Full	185 -186	35 -39 (1-2)	MSD feels that the review question should be expanded to also acknowledge the role of infliximab as an option for the maintenance of remission	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis'

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							<p>and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process. TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	31	Full	235		Regarding point 31 - MSD feels that the role of infliximab as an option for the maintenance of remission should be acknowledged, particularly as patients can become refractory to azathioprine, and therefore require alternative treatments	Thank you for your comment. The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to

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							http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012 . It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.
SH	MSD Ltd	32	Full	242	17-20	The clinical evidence section states that included studies examined immunomodulators (azathioprine, mercaptopurine, ciclosporin) whereas the text on page 243, line 27 refers to a study which examined immunomodulators (azathioprine, mercaptopurine, ciclosporin, infliximab) - there is a discrepancy between the two statements in that one includes infliximab under the description of "immunomodulator" whereas the other does not	Thank you for your comment. Infliximab has been added.
SH	MSD Ltd	33	Full	248		In the grey boxed section "Trade off between clinical benefits and harms", it is stated that included studies examined immunomodulators (azathioprine, mercaptopurine, ciclosporin) whereas earlier text (page 243, line 27) referred to	Thank you for your comment. Infliximab has been added.

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						a study which examined immunomodulators (azathioprine, mercaptopurine, ciclosporin, infliximab) - there is a discrepancy between this and the previous statement	
SH	MSD Ltd	34	NICE	3		Regarding the statement "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 or corticosteroids". MSD kindly suggests biologics such as infliximab should be included in this list of treatment options	Thank you for your comment. 'biological drugs' has been added to the sentence.
SH	MSD Ltd	35	NICE	4		<p>Although this clinical guideline covers children, adolescents, and adults, MSD feels that it would be beneficial to provide more specific information regarding treatment in children and adolescents, particularly as fewer therapeutic options are available to this group of patients</p> <p>The role of infliximab as the only licensed biologic therapy in children and adolescents should be clearly acknowledged, particularly as it is even more desirable for children and adolescents to have access to effective treatments that delay or prevent surgery - which can have long-term consequences; typical post-surgical problems include persistent increased stool frequency (3-10 x/day), bile acid malabsorption, small</p>	<p>Thank you for your comment. The GDG recognised the importance of providing information specific to children and young people and have done so where the evidence allowed this distinction. The GDG noted the paucity of evidence for treatments for young people and children.</p> <p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Updating the TAs was not part of the remit</p>

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						<p>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)</p>	<p>of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA140 review decision (http://guidance.nice.org.uk/TA140/ReviewDecision) noted that the fact that the marketing authorisation for infliximab had been extended to include younger people (aged 6–17 years) and that this fact would be taken into account when NICE scopes its forthcoming multiple technology appraisal of TNF alpha inhibitors.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>

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SH	MSD Ltd	36	NICE	11		Within the section "inducing remission: treating acute severe ulcerative colitis", for the induction of remission the addition of ciclosporin to intravenous corticosteroids or surgery have been considered. However, infliximab has been recommended by NICE in the acute severe population (NICE TA163), and therefore, MSD kindly suggests that infliximab should also be considered	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012 The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.
SH	MSD Ltd	37	NICE	12		Within the section "maintaining remission",	Thank you for your comment. Infliximab has

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						for the maintenance of remission aminosalicylates have been considered. MSD kindly suggests that the role of infliximab as an option for the maintenance of remission should be acknowledged	<p>been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline.</p> <p>The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012.</p> <p>It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>

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SH	MSD Ltd	38	NICE	13 -14		<p>NICE TA140 states that “sub-acute” patients are defined as having “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”</p> <p>This definition is briefly referenced in this clinical guideline. However, MSD notes that no actual guidance is provided within this draft version for the management of patients with moderately to severely active disease, despite the availability of treatments such as infliximab (which have an indication for moderately to severely active ulcerative colitis)</p> <p>As reference, please note that:</p> <p>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</p> <p>Infliximab now has 5 years of licensed experience in ulcerative colitis having</p>	<p>Thank you for your comment.</p> <p>There was extensive discussion by the GDG on the terminology used clinically for people who have symptoms that are at the top range of moderate disease but can be managed in an outpatient setting. In this guideline ‘subacute’ was chosen to describe this population and the definition is based on that used in NICE TA140 ‘Infliximab for subacute manifestations of ulcerative colitis’.</p> <p>This decision was based on the GDG belief that this is a term understood by clinicians, to maintain consistency across NICE guidance and in the absence of any other consistent term in the literature. The GDG also noted if this population was referred to as having ‘moderately to severely active ulcerative colitis’ without further explanation and in the place of subacute then people with severely active ulcerative colitis could be treated inappropriately.</p> <p>The GDG agree it is important that the needs of patients who have symptoms that are at the severe end of the moderate disease category are considered in this guideline. Recommendations 1.1.5 (now 1.2.3), 1.1.8 (now 1.2.6) and 1.1.9 (now 1.2.9) refer to treatment for the subacute</p>

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						<p>gained its license in March 2006</p> <p>In addition, MSD would note that the pivotal clinical trials and the majority of data on the use of infliximab in ulcerative colitis are for the moderately to severely active patient population</p>	<p>population.</p> <p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process.</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented</p>

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							side-by-side with the recommendations in the clinical guideline in the NICE Pathway.
SH	MSD Ltd	39	NICE	13		At this, and at all subsequent references to NICE TA140 throughout the document, MSD feels that it would be beneficial to indicate that this appraisal will be under review in the forthcoming MTA for ulcerative colitis	Thank you for your comment. Infliximab has been reviewed in TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Readers who refer to TA140 'Infliximab for subacute manifestations of ulcerative colitis' can follow the progress of the forthcoming proposed MTA.
SH	MSD Ltd	40	NICE	17		The data supporting the guidance around tacrolimus for the induction of remission relate to two small trials where N=101 and N=41 (referenced on page 151, line 2). These trials were appraised to be of "very low quality" evidence and indicated that there was no clinically important difference between tacrolimus and placebo for the induction of remission, and as such MSD feels that the guidance for its use is unwarranted, particularly as tacrolimus does not have an indication for this usage	<p>Thank you for your comment. Thank you for your comment.</p> <p>The GDG recognise that the evidence for all the immunomodulators reviewed is limited and of very low quality. This made any decision on the use of immunomodulators difficult. However the GDG considered it was important to have a treatment option for patients that are refractory to systemic steroids. The GDG decided to recommend tacrolimus over the use of other immunomodulators for the following reasons; the lack of evidence to support the use of methotrexate, the GDG felt azathioprine takes too long to have an effect and its role is limited for induction of remission and in people who have not responded to prednisolone, and</p>

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							the GDG noted benefit of tacrolimus (Ogata et al 2006;Ogata 2012). The GDG acknowledged that nephrotoxicity and opportunistic infections may be an issue with longer term use of tacrolimus and recommended regular monitoring. This is reported in the 'trade of between clinical benefits and harms' section of the induction
SH	MSD Ltd	41	NICE	17 -18		<p>Within the section "treating acute severe ulcerative colitis: all extents of disease" (through to page 18), MSD feels that the role of infliximab should be stated more clearly, rather than solely referring users to the separate NICE TA163 document</p> <p>MSD kindly suggests that additional wording is included to explain the role of infliximab more clearly, for instance, through acknowledging that infliximab provides an additional option for treatment in line with its indication (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)</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process. TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959</p>

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							/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012 The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.
SH	MSD Ltd	42	NICE	21 -22		Within sections 1.3.4 and 1.3.5 MSD kindly suggests that the role of infliximab as an option for the maintenance of remission should be acknowledged	Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012 . It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in induction were completed. The GDG noted

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							<p>that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	43	NICE	22		<p>Within section 1.3.6 MSD feels that the role of infliximab as an option for the maintenance of remission should be acknowledged, particularly as patients can become refractory to azathioprine, and therefore require alternative treatments</p>	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline.</p> <p>The novel use of biologics is not usually reviewed in NICE clinical guidelines and has previously been referred to the NICE technology appraisal programme. In line with this, Technology Appraisals 140 AND 163 are being updated on the use of anti-TNFs in the induction of remission. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012.</p> <p>It would have been inappropriate for a review to be undertaken on the use of infliximab for the maintenance of remission in ulcerative colitis before these updates in</p>

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							<p>induction were completed. The GDG noted that infliximab is not licensed for use in the maintenance of remission in ulcerative colitis. As infliximab was not reviewed, the GDG could not make a recommendation.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	MSD Ltd	44	NICE	24 -25		The first and second research recommendations (sections 2.1 and 2.2) refer to moderate populations which is inconsistent with the language used in the rest of the clinical guideline (where mild to moderate disease is considered, but not moderate alone)	Thank you for your comment. The paucity in the evidence is in the moderate disease population where you would be considering the choice between ASA and prednisolone. Prednisolone would be less likely to be a treatment option with mild disease. Please refer to Appendix M which provides the GDG's rationale for formulating the research recommendations.
SH	MSD Ltd	45	NICE	26		<p>The third key research recommendation (section 2.3) questions the benefits, risks, and cost-effectiveness of methotrexate, ciclosporin, tacrolimus, and infliximab</p> <p>Given that clinical and cost-effectiveness evidence is already available for infliximab, MSD kindly suggests that this evidence be included within this clinical guideline</p>	<p>Thank you for your comment. Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Updating the TAs was not part of the remit of the scope or the guideline.</p> <p>Due to the funding directive applied to technology appraisal guidance, unless there</p>

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							<p>is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process</p> <p>TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors.</p> <p>Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p>
SH	Neonatal and Paediatric Pharmacists Group (NPPG)	1	NICE	24		Research Recommendation 2.1 – we are pleased to see that the text makes it clear that this is an important issue in children and that the proposed research will include this population.	Thank you for your comment.
SH	Neonatal and Paediatric Pharmacists Group (NPPG)	2	NICE	26		Research Recommendation 2.3 – it is disappointing that the trial proposed is only to be undertaken in adults.	Thank you for your comment. We have added another FRR that covers children and takes into account the different outcome measures that are important to children.
SH	NHS Direct	1	Full	General		NHS Direct welcome this guideline and have no comments on its content.	Thank you for your comment.
SH	NHS Dorset	1	Full	General		Thank you for the opportunity to comment on this Clinical Guideline which covers an	Thank you for your comment. The areas covered by the guideline were defined by

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						important clinical issue. The guideline pulls together a very comprehensive overview of early steps in managing this disease supported by in depth, complex analysis to understand the most clinical and cost-effective treatment pathways. A number of questions or gaps remain unanswered however, particularly for patients at the more severe end of the spectrum.	the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended. Recommendations 1.1.12 (now 1.2.10) to 1.1.19 (now 1.2.17) and 1.3.6 (now 1.4.5) refer to treatment for people with acute severe colitis.
SH	NHS Dorset	2	Full	General		Particularly helpful are the sections in grey at the end of the recommendations tables in which the trade offs between clinical benefits and harms are discussed.	Thank you for your comment.
SH	NHS Dorset	3	Full	General		Although anti-TNFS are now used widely in the treatment of ulcerative colitis, you refer to TA 163 in respect of these drugs. This guidance, published in 2008, was due for review in Dec 2011 and at that time review of the TA was postponed until the GETAID CYSIF study, the CONSTRUCT study and the adalimumab in progress TA were published. CYSIF has now been published (Laharie et al. Lancet, v 380, iss 9857: 1909-1915) and shows that there was no significant difference between ciclosporin and infliximab on treatment failure but infliximab pateinst had more adverse effects. The publication of CONSTRUCT is delayed until 2015, and	Thank you for your comment. Infliximab has been reviewed in TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross-referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process. TA140 'Infliximab for subacute

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						the adalimumab TA was terminated July 2012 because of no manufacturer submission. This review is therefore now a priority as there are diverging views between treating clinicians and clinical commissioners about the adverse effects of ciclosporin compared to anti-TNFs and their place in treatment.	manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal, including other tumour necrosis factor (TNF) alpha inhibitors, and the terminated appraisal 'Adalimumab for the treatment of moderate to severe ulcerative colitis (TA262). NICE will also request a referral for an appraisal of golimumab for ulcerative colitis to be included in this multiple technology appraisal. See http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012
SH	NHS Dorset	4	Full	General		Within the scope for the guideline 3.3.1b refers to Indications and timing for surgical management. Although the guideline does cover indices to determine likelihood of surgery and information patients need for surgery, this does not address the issue raised in the scope around timing of surgery particularly for patients with recurrent relapses or continuing uncontrolled sub acute symptoms.	Thank you for your comment. The GDG discussed this issue at length and decided it was important that patients with recurrent relapses or continuing uncontrolled subacute symptoms have information to help them decide whether surgery is an option for them and on the timing of surgery. This has been addressed in the information on surgery review. It is important that this population has the right information to make this decision. The information for surgery in the guideline is written for people having elective surgery but the principles can be applied to people requiring emergency surgery. We have added a paragraph in the clinical introduction of chapter 6 to highlight this aim (section 6.1).
SH	NHS Dorset	5	Full	General		In section 5, you do not consider the issue	Thank you for your comment. The GDG did

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				ral		of arsenic used as a suppository in patients with proctitis. We have had a number of requests to support the use of this drug in individual patients. Given that this is not covered by the guideline I presume that you were unable to find any evidence to support its use in this context.	not prioritise arsenic suppositories as a treatment to induce remission when identifying treatments to compare in the review. The GDG noted that with arsenic suppositories there is a potential for serious toxicity and they are infrequently used in the treatment of acute ulcerative colitis. The GDG prioritised treatments that were more commonly used. As arsenic suppositories were not reviewed, the GDG could not make a recommendation on them.
SH	NHS Dorset	6	Full	General		Section 8: Pregnant women. This provides a comprehensive consideration of the impact of medical management in pregnant women, in terms of pregnancy outcomes and highlights that there is no clear evidence of any harm from any specific treatments, but that pregnant women should be given appropriate information to make an informed choice. Given that NICE have already conducted an extensive review of this evidence and have experience in pulling together information for patients in a clear and understandable format, a key tool for implementing this guideline might be a patient information pack from NICE summarising these issues.	Thank you for your comment. NICE will produce an 'Information for the public' version of the guideline. We will pass on the suggestion to produce a patient information pack specifically for pregnant women with ulcerative colitis to the Implementation team at NICE.
SH	NHS Dorset	7	Full	General		Section 8: Pregnant women. Although this section applies to pregnant women, the information within it may be relevant to all women of child-bearing age, and this	Thank you for your comment. The scope included pregnant women as a group for special consideration and the review undertaken in section 8 specifically

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						should be clarified within the section.	considered the consequences of using drug treatments in pregnant women, therefore any conclusions made can only be applied to this population. Please refer to recommendation 1.1.2. Preconceptual care was not included in the scope and was not considered in the guideline. Preconceptual care was not included in the scope as it was not prioritised in the scope consultation or stakeholder workshop. Any woman considering pregnancy should discuss any concerns that she may have with her clinicians.
SH	NHS Dorset	8	Full	General		Section 8. This section does not address the issue of surgery, including pre-conception surgery for UC on pregnancy outcomes, presumably because of limited evidence in this area.	Thank you for your comment. The review undertaken in section 8 specifically considered the consequences of using drug treatments in pregnant women, therefore any conclusions made can only be applied to these treatments. Recommendation 1.1.12 (now 1.2.10) highlights the need to include the obstetric and gynaecology team when pregnant women are admitted to hospital with acute severe disease and where surgery may be an outcome. Please also refer to the chapter on information on surgery. Preconceptual care was not included in the scope and was not considered in the guideline. Preconceptual care was not part

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							of the scope as it was not prioritised in the scope consultation or stakeholder workshop. As these topics were not reviewed the GDG could not make a recommendation on them. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.
SH	NHS Dorset	9	Full	General		Section 8. This section does not address the issue of UC management on conception rates, again presumably because of limited evidence in this area.	Thank you for your comment. Please refer to recommendation 1.1.2. Preconceptual care was not included in the scope and was not considered in the guideline. Preconceptual care was not part of the scope as it was not prioritised in the scope consultation or stakeholder workshop. As these topics were not reviewed the GDG could not make a recommendation on them. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.
SH	NHS Dorset	10	Full	53	14	Table 8 - does not fit on page – only part visible	Thank you for your comment. We have made this change.
SH	NHS Dorset	11	Full	141	15	Table 59 – I am unclear what the 'inpatient' element of the treatment strategy means. Is this about delivering	Thank you for your comment. Patient failing to respond to prednisolone were assumed to have progressed to more severe disease

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						the same medications but in an inpatient setting as planned admission or about converting to acute exacerbation and managing in line with that.	that would need inpatient admission. Inpatient refers to the stage in the pathway when patients are admitted to hospital.
SH	NHS Dorset	12	Full	186	7	Table 76 – does not fit on page – only part visible	Thank you for your comment. We have made this change.
SH	NHS Dorset	13	NICE	8		It is very helpful to outline how you express the strength of your recommendations in this way.	Thank you for your comment.
SH	NHS Dorset	14	NICE	26		Research recommendation 2.3. Induction of remission in patients with subacute UC. This is a very important research question and one where clinical practice appears to be changing despite the lack of a formal evidence base.	Thank you for your comment.
SH	Pharmacosmos A/S and Pharmacosmos UK	1	Full	General		Our comments are as follows: In the NICE's Ulcerative Colitis guideline, treatment of anaemia is not included. As anaemia is a very common condition/disease among patients diagnosed with inflammatory bowel disease (IBD) we suggest including a section about anaemia into this new version of the guidelines. According to a survey by J Stein et al. (attached) performed in 2009 and a follow-up in 2011 (JCC, Vol. 6 Suppl. 1, S151-S152, 2012) about anaemia management in patients with IBD, the treatment practice in several countries (incl. UK) is not in line with the treatment recommendations and it did not change from 2009 to 2011 despite	Thank you for your comment. The treatment of anaemia was not included in the scope and was not considered in the guideline. As these topics were not reviewed the GDG could not make a recommendation on them. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended. During the scope consultation the decision not to include anaemia was based on the following reason: anaemia is a manifestation of many chronic conditions,

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						new clinical data. By including a chapter about how to treat anaemia in patients diagnosed with Ulcerative Colitis the NICE organisation can make a difference for these patients by increase awareness on the importance of treating anaemia in these kinds of patients.	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.
SH	RCOG	1	Full	General		Chapter 8 of the guideline attempts to address the key issues relating to pregnant women with UC. Suggest change foetal to fetal, and replace abortion with miscarriage.	Thank you for your comment. We have made this change in the clinical introduction.
SH	RCOG	2	FULL	249		The clinician is looking for guidance regarding what is safe and effective to prescribe in pregnancy. The available studies are considered to be of too low quality to generate such guidance. The inability of the GDG to make a recommendation regarding the potential harm or benefit of drug treatments in pregnant women with UC is highlighted in the Full guideline but not in the NICE version. I consider this inability to be an important outcome of the guideline development process since it openly acknowledges that there is no optimal treatment. The recommendations in both the NICE and full versions are inevitably bland as a consequence of the poor data. I would like to see the GDG's inability to make a recommendation included in the	Thank you for your comment. The full guideline provides the methods, evidence and recommendations. The NICE version reproduces the list of recommendations from the full guideline verbatim. The GDG's consideration of the evidence is provided in the 'recommendations and link to evidence' tables in the full guideline and are not usually reproduced in the NICE version. The strength of the recommendation is a reflection of the GDG's consideration of the evidence available.

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						NICE version for those readers who will consult NICE but not Full versions; such an inclusion will reassure the reader (of the NICE version) that the matter of optimal drug treatment has been fully considered, something that is not readily apparent when reading the current NICE version.	
SH	RCOG	3	Appendix M	General		Support the research proposal to generate a prospective register of women with UC who become pregnant.	Thank you for your comment.
SH	RCOG	4	Full	Chapter 8		Methotrexate is specifically excluded as a treatment option (entirely appropriate) but some mention of the suitability or otherwise of some of the other less widely used drugs would be helpful to obstetricians ie cyclosporine, azathioprine, TNF alpha inhibitor.	Thank you for your comment. After reviewing the evidence the GDG did not feel confident in commenting on specific treatments for use in pregnant women. The rationale for this is detailed in the recommendations and link to evidence box (section 8.6).
SH	Roche Products Limited	1	NICE	general	general	We would support further research into the effect that surgery (particularly urgent surgery) has on a patient's quality of life. Clinicians in TA140/163 identified the importance of delaying urgent surgery in order for patients to come to terms with the lifelong consequences of the operation. TA163 noted the significant improvement in a patient's quality of life associated with delaying and where possible avoiding surgery. We would welcome further research into the quality of life of patients with severe UC, and the	Thank you for your comment. The GDG agree that the psychological needs of people undergoing surgery are important however they do not agree that it is appropriate to delay surgery in people with severe ulcerative colitis who are not responding to treatment. The use of infliximab plays a role in avoiding surgery and quality of life would be an appropriate outcome in a study evaluating this. The use of infliximab as a rescue therapy after people have not responded to

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						<p>significant improvements associated with avoiding urgent surgery.</p> <p>We would also recommend research into the costs associated with surgery/colectomy. We know that post-surgery costs related to a colectomy can accrue well into the future and further research is needed to quantify these costs accurately.</p>	intravenous corticosteroids has been addressed (for example see Laharie D, Bourreille A, Branche J, et al. Cyclosporin versus infliximab in severe acute ulcerative colitis refractory to intravenous steroids: a randomized trial. Lancet . 2012 Dec Epub 2012 Oct 10.). The GDG agree that cost effectiveness studies are important.
SH	Royal College of Nursing	1	General	General		The Royal College of Nursing welcomes this guideline. It seems comprehensive.	Thank you for your comment.
SH	Royal College of Nursing	2	Full	10 & 11	general	<p>The way in which the key messages are laid out suggests that the clinician goes from topical therapy in mild to moderate disease with an escalation to ciclosporin in severe disease. Although this is clearly not the intended treatment pathway having read the rest of the document.</p> <p>There is no mention in the key messages of using prednisolone.</p>	Thank you for your comment. Section 4.2 'Key priorities for implementation' are the recommendations that the GDG has selected as being the recommendations that are most likely to have a high impact on patients' outcomes and on reducing variations in clinical management (in accordance with the NICE Guidelines manual referenced in the introductory paragraph of section 4.2); it is not a simple summary of section 4.3 (which provides the full list of recommendations).
SH	Royal College of Nursing	3	Full	10 and 11	general	We are pleased to see the use of clipper though, we are aware of colleagues who have used it and have often found it effective.	Thank you for your comment.
SH	Royal College of Nursing	4	Full	general		There does not appear to be any mention of arsenic suppositories?	Thank you for your comment. The GDG did not identify arsenic suppositories as a treatment to induce remission and as such were not included in the review of

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							treatments. As these topics were not reviewed the GDG could not make a recommendation on them. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended. Arsenic suppositories were not identified as an area to address by stakeholders during this time.
SH	Royal College of Paediatrics and Child Health	1	Full	40 and 42	Algorithm 2 and 4.2	<ol style="list-style-type: none"> 1. Ciclosporin is recommended as an alternative to surgery. The role of Infliximab is not discussed but referred to NICE guidance 163 which only recommends Infliximab if ciclosporin is contraindicated, clinically inappropriate or as part of clinical trials. 2. Ciclosporin requires monitoring of blood levels. It has a narrow therapeutic range with extreme toxicity at higher levels and a poor response at lower levels. 3. The NICE guidance 163 is outdated (2008) and recent evidence suggests that Infliximab is at least as effective as ciclosporin not only in inducing remission but also maintaining it. ("Outcome following infliximab therapy in children with ulcerative colitis". Hyams JS et al, Pediatric Inflammatory 	<p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors.</p>

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						<p>Bowel Disease Collaborative Research Group, Am J Gastroenterol. 2010;105(6):1430; CONCLUSIONS: by 24 months, 61% of patients had avoided colectomy</p> <p>4. "Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis". Hyams J et al, T72 Study Group. Clin Gastroenterol Hepatol. 2012; 10(4):391. CONCLUSIONS: Infliximab was safe and effective, inducing a response at week 8 in 73.3% of paediatric patients with moderate to severely active UC who did not respond to conventional therapy)</p> <p>5. Presently, Commissioning Groups are guided by the NICE guideline and Infliximab in this setting is denied to many children. It is imperative that it is mentioned as an alternative to ciclosporin for children outside the NICE 163 guideline.</p>	<p>Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA140 review decision (http://guidance.nice.org.uk/TA140/ReviewDecision) noted that the fact that the marketing authorisation for infliximab had been extended to include younger people (aged 6–17 years) and that this fact would be taken into account when NICE scopes its forthcoming multiple technology appraisal of TNF alpha inhibitors.</p> <p>The TA recommendations will be presented side-by-side with the recommendations in the clinical guideline in the NICE Pathway.</p> <p>The GDG recognise the limited evidence base of ciclosporin and discuss this in the 'trade off between clinical benefits and harms' section in the Recommendations and link to evidence box for inducing remission in acute severe disease in chapter 5.</p> <p>The GDG recognised the need to monitor ciclosporin and this is stated in</p>

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							recommendation 1.2.15 (final recommendation numbering).
SH	Royal College of Paediatrics and Child Health	2	Full	42	21	“After surgery , ensure that a specialist who is knowledgeable about stomas gives the person information about managing the effects on bowel function”. In children, this should be before surgery as part of the discussion regarding surgical options, and not afterwards.	<p>Thank you for your comment. Pages 41-42 of the full guideline provide the ‘key priorities for implementation’. Please refer to the full list of recommendations provided in section 4.3; recommendation 24 (now 25) addresses this point.</p> <p>Recommendation 25 (now 26) of the full guideline highlights the need for people to have information on stoma when they are considering surgery.</p>
SH	Royal College of Paediatrics and Child Health	3	Full	15	39 /40	This guideline covers all patients with UC, i.e. children and adults. It does not seem to emphasize the need for children with IBD to be under the coordinating care of a paediatric gastroenterologist. Without this clear recommendation there is a danger that children could be managed by adult colorectal surgeons or gastroenterologists in the DGH setting without appropriate consideration to growth or development and without the appropriate knowledge of how IBD differs in children. Children with UC need to be seen at least annually in a tertiary centre by a paediatric gastroenterologist irrespective of the length of apparent remission. In addition, they need more regular review (every 3 to 4 months) by a consultant with expertise in	<p>Thank you for your comment. The GDG agrees that it is important that young people and children are cared for by an appropriate team.</p> <p>The GDG did not look at specific evidence about the specific composition of the MDT but have highlighted in recommendations 1.1.1 and 1.2.10 ‘ensure the composition of the multidisciplinary team is appropriate for the age of the person’ and recommendation 1.2.10 directly refers to seek advice from a paediatrician with expertise in gastroenterology when treating a child or young person.</p> <p>These recommendations are clear that children should not be managed by adult colorectal surgeons or adult gastroenterologists. However it could be the case in a DGH that a child is under the care</p>

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						gastroenterology or alternatively a paediatric gastroenterologist (depending on the local arrangements). Networks for children with IBD may include an adult gastroenterologist as well as a local paediatrician with a special interest.	<p>of a paediatrician who is advised by a paediatric gastroenterologist.</p> <p>The GDG considered that naming the specific members of the MDT was a service delivery issue and could have significant impact on resources.</p> <p>The general follow-up and review of children and young people was not included the scope. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.</p> <p>The monitoring of bone health and growth has been addressed in chapter 9 and recommendations 1.5.2 (now 1.6.2) and 1.5.3 (now 1.6.3) are specific to children and young people.</p>
SH	Royal College of Paediatrics and Child Health	4	Full	41 /42		Sections 4.2 and 4.3 are a bit confusing. 4.2 'Key priorities for implementation' simply summarises a lot of the second section, but misses out important information, such as infliximab recommendations. It may be better to have the complete part first, or, to introduce the first section completely so it clearly shows that only part of the whole	Thank you for your comment. Section 4.2 'Key priorities for implementation' are the recommendations that the GDG has selected as being the recommendations that are most likely to have a high impact on patients' outcomes and on reducing variations in clinical management (as per the NICE Guidelines manual referenced in the introductory paragraph of section 4.2); it

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						document is being mentioned.	is not a simple summary of section 4.3 (which provides the full list of recommendations).
SH	Royal College of Paediatrics and Child Health	5	Full	41 /42	(foot notes)	The GMC request fully informed documented consent for all off label medicines. This has major implications (probably unrealistic) for paediatrics and we do not think this has been applied in this way in other NICE guidelines.	Thank you for your comment. It is NICE's standard practice, as agreed with the MHRA, to append a footnote to all off-label recommendations in all NICE clinical guidelines.
SH	Royal College of Paediatrics and Child Health	6	NICE	16	1.1.10	For children and young adults with mild/moderate UC that is failing to respond to anti-inflammatory therapy, a delay of 4 weeks would be rather long before moving to step 2. Although not evidence-based, most practice would likely step up after a maximum of 2 weeks if there was a lack of response.	Thank you for your comment. We agree with these comments and phrased the recommendation to indicate treatment could be stepped up <i>within</i> 4 weeks. This would allow treatment to be stepped up after a maximum of 2 weeks as suggested.
SH	Royal College of Paediatrics and Child Health	7	NICE	17	1.1.11	Oral tacrolimus is an uncommon choice as a third line therapy in children to induce remission. It is much more likely that early addition of a thiopurine would be encouraged, with prolonged steroid tail to reach thiopurine efficacy. Failing to include biological therapies such as Infliximab directly means that the guideline is already out of date and partly redundant. The use of Infliximab is referenced within the text of this guideline in other NICE guidance e.g. NICE TA 163 (2008). It seems illogical that this has not been "dovetailed" in to this guideline. It would be far simpler if Infliximab were included and there was	<p>Thank you for your comment. The evidence-base for the role of these treatments in the induction of remission is limited in all age groups. The GDG has reflected this absence of evidence in the recommendations and in the 'trade off between clinical benefits and harms' under the heading immunomodulators in the Recommendations and link to evidence box (section 5.40).</p> <p>Thank you for your comment. Infliximab has been reviewed in NICE technology appraisal guidance TA140 'Infliximab for</p>

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						<p>clarity as to when in the various algorithms e.g. refractory chronic UC or acute severe UC Infliximab can or should be given.</p>	<p>subacute manifestations of ulcerative colitis' and TA163 'Infliximab for acute exacerbations of ulcerative colitis' which have been cross referred to in the guideline. Updating the TAs was not part of the remit of the scope or the guideline. Due to the funding directive applied to technology appraisal guidance, unless there is sufficient reason given by stakeholders justifying inclusion in a clinical guideline, new technologies are generally appraised in the technology appraisal process TA140 'Infliximab for subacute manifestations of ulcerative colitis' will be updated in the context of a multiple technology appraisal that includes other tumour necrosis factor alpha inhibitors. Refer to http://www.nice.org.uk/nicemedia/live/11959/61293/61293.pdf and http://guidance.nice.org.uk/TA140/ReviewDecisionOctober2012</p> <p>The TA140 review decision (http://guidance.nice.org.uk/TA140/ReviewDecision) noted that the fact that the marketing authorisation for infliximab had been extended to include younger people (aged 6–17 years) and that this fact would be taken into account when NICE scopes its forthcoming multiple technology appraisal of TNF alpha inhibitors.</p>

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							<p>The TA guidance will be presented side by side with the recommendations in the guideline in the NICE Pathway.</p> <p>The cross-reference has been amended to make the relationship of infliximab to ciclosporin clear.</p>
SH	Royal College of Paediatrics and Child Health	8	NICE	18	1.1.1 8	Using the well validated PUCAI to assess response to therapy in children with acute severe UC is now a national recommendation from BSPGHAN. The evidence for using the PUCAI is strong and much better validated than any other score available. It is simple and non-invasive and widely used. We think this is what should be used for our patients.	Thank you for your comment. We have included the PUCAI as the tool to assess the severity of ulcerative colitis in young people and children. In reference to assessing the likelihood of needing surgery the GDG has addressed this issue in the 'other considerations' section of the Recommendations and link to evidence box (section 5.53). 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 only one study was identified this compared the PUCAI to other indexes, a derivation study was not identified.
SH	Royal College of Paediatrics and Child Health	9	Full	41	6	For children and young people it would be worth specifically mentioning information available from CICRA and NACC.	Thank you for your comment. The full guideline contains the methods, evidence and recommendations.
SH	Royal College of Paediatrics and Child Health	10	Full	51		UC is not the most common form of IBD in children and when children are diagnosed with UC they are more likely to have a pancolitis than adult patients. The definition of acute severe colitis should be	Thank you for your comment. The GDG agree that sending stools for C&S, C. difficile and considering biopsy and blood for CMV when a person has relapsed is an important part of the management of people

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						made by paediatric specific tool. As above, the only validated instrument is the PUCAL. It must be made clear in the guideline that patients hospitalised with acute severe colitis need to have stool tested for C Diff on admission and at least every week thereafter.	with UC. However these areas were not part of the scope. These areas were not part of the scope as they were not prioritised in the scope consultation or stakeholder workshop. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended. The areas covered by the guideline were defined by the scope. The draft scope was informed by stakeholder comments at a workshop held in May 2011 and then opened up to public stakeholder consultation in June–July 2011, after which the scope was amended.
SH	Royal College of Paediatrics and Child Health	11	Full	49	8	Recommendation 35 is too vague. "Consider" should not be used in a recommendation sentence by NICE. The GDG should clearly advocate either the monitoring of bone health with details or not in the specific circumstances described.	Thank you for your comments. Recommendation 35. The GDG recognised the importance of monitoring bone health however the evidence identified in this area was sparse and of low quality. The GDG note in this in the 'other considerations' section of the Bone health Recommendations and link to evidence box (section 9.7) and how this is reflected in the strength of the recommendation. Please refer to page 8 of the NICE version which explains the strength of NICE recommendations. See

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							also Chapter 9 of the NICE guidelines manual sets out the process for GDGs deciding the strength of recommendations and how they are worded, http://publications.nice.org.uk/the-guidelines-manual-pmg6/developing-and-wording-guideline-recommendations .
SH	Royal College of Paediatrics and Child Health	12	Full	49	15	Monitoring growth every 6 or 12 months in children going through puberty is not sufficient. They need to be seen at least every 4 months in a consultant clinic where the child's growth is assessed. Maximal growth velocity may only last for 2 years and if you leave it for 12 months before discovering that this is sub-optimal it does not give sufficient time to intervene successfully with either a medical escalation or surgery. This is the time when it is essential that children and young people are being reviewed regularly by expert tertiary paediatric gastroenterologists.	<p>Thank you for your comment.</p> <p>Recommendation 36 The timing of monitoring growth was reviewed and no evidence was identified to support the GDG in their decision making. This issue was discussed at length by the GDG. These discussions are summarised in the 'other considerations' section of the Recommendations and link to evidence box of chapter 9. Notably the GDG recognised the difficulties of accurately and reliably measuring growth and the consequences of measuring growth too frequently (measurement error) but considered the benefits of monitoring growth regularly outweighed any potential risks of infrequent sporadic monitoring. The GDG discussed the optimal frequency of monitoring growth in children and young people and in the absence of evidence considered disease activity to be a reasonable marker for defining frequency. The more severe the disease activity, the use of systemic steroids and during puberty the greater the</p>

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							potential for growth delay. This has been reflected in the recommendation to highlight that monitoring should be done 'every 6 months during pubertal growth if the disease is inactive'.
SH	Royal College of Paediatrics and Child Health	13	Full	49	24	This is unrealistic and will not result in effective growth monitoring. Children need to be measured in a standard way, using the correct equipment, in the same setting and by appropriately trained staff. The height and weights then need to be plotted on appropriate centile charts in the case notes and reviewed by the responsible clinician. Senior clinical continuity and coordinating responsibility is essential. Random measurements taken and recorded in different settings will not equate to effective growth monitoring. This point is of crucial importance as commissioners may lose sight of the need for expert, regular tertiary involvement in this potentially vulnerable group.	<p>Thank you for your comment.</p> <p>Recommendation 37 (now recommendation 39) The GDG were keen to convey the message that young people and children should have their growth monitored regularly. But as noted in the Recommendations and link to evidence box (section 9.13) there was not any evidence identified on the optimal strategies for monitoring. The GDG considered that naming a location or a specific professional to undertake monitoring would be unhelpful in implementing this recommendation but have emphasised should be carried out by appropriately trained professionals. Recommendation 39 also now states monitoring should be done as part of the overall clinical assessment, including disease activity, to help inform the need for timely investigation, referral and/or interventions, particularly during critical phase of pubertal growth. The recommendations have been reordered to reflect the measurements should not be done in isolation.</p>

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SH	Royal College of Paediatrics and Child Health	14	Full	49	37	Children should already be under the care of a tertiary paediatric gastroenterologist with or without shared care with a consultant paediatrician with a special interest/post graduate expertise in the care of paediatric IBD. This does not seem implicit in this recommendation.	<p>Thank you for your comment. Recommendation 41 (now recommendation 38):</p> <p>The GDG agree that children should already be under the care of a tertiary paediatric gastroenterologist with or without shared care with a consultant paediatrician with a special interest / post graduate expertise in the care of paediatric IBD. This recommendation does not reflect on the overall general care and who young people and children should be under the care of but specifically to pubertal delay.</p> <p>The recommendations on monitoring of growth and pubertal delay note that monitoring can take place at routine appointments, acute admissions or urgent appointments in primary care, community services or secondary care.</p> <p>The aim of this recommendation is to ensure that young people with delayed pubertal development have a timely referral to someone either with the access to or the expertise to investigate pubertal delay.</p>
SH	Royal College of Physicians	1	Full	General		RCP wishes to fully endorse the comments submitted by the BSG to the above consultation.	Thank you for your comment.
SH	Royal College Radiologists and	1	Full	175	14	We agree with the GDC that the various indicies available are poorly validated and a pragmatic approach must be taken. In terms of radiology the comments	No evidence was identified for CT or MR imaging and the GDG considered in the absence of this evidence it would be difficult to comment on their use in this situation.

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	British Society of Gastrointestinal and Abdominal Radiology					regarding appearances on abdominal x-ray appear sensible. However it would be very helpful to include a brief comment regarding cross sectional imaging particularly in cases with increasing abdominal pain. Both CT and MR imaging offer a high sensitivity to complications such as perforation and collection as well as to an assessment of colonic wall thickening and degree of inflammation. MR has the advantage of no ionising radiation and offers superior views of the pelvis.	
SH	Shire Pharmaceuticals	1	Full	39		<p>In the algorithm is there scope for comment with regards to “optimising 5’ASA therapy” at step 2 before escalating to addition of steroids?</p> <p>Failure to optimize conventional therapy could lead to a potentially effective treatment being abandoned too early. Patients could then be unnecessarily exposed to potentially more toxic entities further down the treatment algorithm. Comment could include enquiry about and encouragement of patients’ adherence to drug dosage schedules. Measures that improve adherence, such as changing to once-daily dosing and decreasing pill burden. Also potentially extend the treatment period or switch the 5’ASA. Maximizing of doses in patients who fail to</p>	<p>Thank you for your comment. The evidence reviews for the induction of remission included variables that addressed the issue of optimisation of aminosalicylate therapy (dose, formulation, regime, mode of delivery and interclass comparisons where possible). When reviewing the evidence and balancing the benefits and harms of different treatments the GDG did not find any compelling evidence that indicated there was another choice of treatment before steroids</p> <p>The GDG were mindful of the move to steroids and the side effects but also acknowledged the delay in moving to steroids when no benefit for optimisation had been identified. This was supported by the economic model. The rationale is summarised throughout the</p>

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						achieve remission or during disease flares. Currently the algorithm mentions starting at a high dose but not maximising this. Optimisation could be considered in people who fail to respond to induction treatment with these agents, and second, in people who relapse while receiving maintenance therapy.	<p>Recommendations and link to evidence box (section 5.40).</p> <p>The dose recommended is already a high dose and no clinical differences were found between formulations or release characteristics. Patient choice is highlighted in recommendations 1.2.1 to 1.2.6 on induction therapy.</p> <p>Recommendation 1.1.2 specifically refers to the importance discussing 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 and refers to Medicines adherence (NICE clinical guideline 76).</p>
SH	Shire Pharmaceuticals	2	Full	44	18	<p>Comment – “Once daily dosing is recommended for maintenance treatment in patients with all extents of disease.” Page 48 line 10.</p> <p>Should this comment at line 10 not apply also in the acute setting as well at page 44 line 18?</p> <p>Trials in the acute and maintenance phase suggest that once daily dosing is effective (Kamm et al Gastroenterology 2007;132:66-75. Kamm et al Gut 2008; 57:893-902). The draft guideline suggests</p>	<p>Thank you for your comment. The GDG recognised the impact of pill burden and treatment adherence and reviewed the evidence on dosing regimens in induction treatments. Unfortunately there was limited evidence comparing dosing regimens in the induction of remission. In addition to the limited evidence, the evidence only 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</p>

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						once daily dosing only in the maintenance phase. In the acute setting as well, this would simplify dosing regimes particularly as patients have an increased tablet burden at this point (increased 5'ASA plus the addition potentially of steroids) Patients in the UK receiving three times a day therapy with 5'ASA is still common.	two situations with regard to the optimum mucosal level of aminosaliclates and differences in transit time and luminal pH which may affect the release of 5-aminosalicylic acid. The GDG were not confident making a recommendation on dosing regimes during induction and felt that this decision should be made with the patient and taking into account the costs and likelihood of adherence.
SH	Shire Pharmaceuticals	3	Full	48	12-13	"...once daily dosing can be more effective, but may result in more side effects." With regards to once daily dosing being associated with an increase in side effects. This wasn't demonstrated in the maintenance trial conducted by Kamm et al (Gut 2008; 57:893-902) with regards to 2.4grams of MMX given as once per day or twice per day over 12 months. In this trial there was no significant difference shown with regards to side effects between the two dosing strategies which is a trend seen with other 5'ASA trials comparing once per day and twice per day dosing as well.	Thank you for your comment. The review and meta-analysis shows that there are more adverse events (RR 1.12, 95% CI 1-1.26) and serious adverse events (RR 1.61, 95% CI 1.03-2.53) and with once- daily dosing (see table 93). Kamm et al (2008) was included in both meta analyses.
SH	Shire Pharmaceuticals	4	Full	111	1	5.18.1.3 Dose comparison 1 - MMX (mesalazine) lines 1-12 – regarding the	Thank you for your comment. The evidence statements summarise the combined

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					-12	<p>difference between MMX 2.4grams and 4.8grams.</p> <p>Analysis from the studies by Kamm (Gastroenterology 2007: 132:66-75) and Lichtenstein et al (Clinical Gastroenterology and Hepatology 2007;5:95-102) of both the primary and secondary outcome measures revealed no apparent dose–response relationship for MMX mesalazine (2.4 vs. 4.8 g/day) in the overall study population; however, it should be remembered that these studies were not powered to detect differences between the active treatment arms. Small numerical advantages were observed at the higher dose for some outcome measures (listed below), but the differences between the two doses were not statistically significant.</p> <p>[Stool frequency and rectal bleeding scores at end point (intention-to-treat population). Improvement in sigmoidoscopy scores and Physician's Global Assessment scores (PGA) at end point (intention-to-treat population) Mean change in total modified Ulcerative Colitis-Disease Activity Index score from week 0 to end point (intention-to-treat population)]</p> <p>WJ Sandborn et al Aliment Pharmacol Ther 2007; 26, 205–215.</p>	evidence not individual studies. The statements include the GDG's conclusions about clinically important findings identified in the analysis not statistical significance. Please refer to chapter 3 on how clinical importance is defined.

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						Other induction studies of oral mesalazine in UC have also failed to demonstrate a clear and consistent dose– response effect above doses of 1.5 g/day. <i>Sandborn WJ. Treatment of ulcerative colitis with oral mesalamine: advances in drug formulation, efficacy expectations and dose response, compliance, and chemoprevention. Rev Gastroenterol Disord 2006; 6: 97–105.</i>	
SH	Shire Pharmaceuticals	5	Appendix A to E	42		<p>Appendix C Section 3.2 Induction of remission NMA (also on page 43 section 3.3)</p> <p>“4.8g mesalazine (MMX) has been excluded from the NMA as it did not demonstrate a dose effect in the clinical review and was thought to have the same effect as 2.4g mesalazine (MMX) at a greater cost and risk of more adverse events”</p> <p>From the trials by Kamm et al (Gastroenterology 2007: 132:66-75) and Lichtenstein et al (Clinical Gastroenterology and Hepatology 2007;5:95-102) when comparing the 2.4gram dosing regime with the 4.8gram there was no significant difference in adverse event profiles in these studies.</p>	<p>Thank you for your comment. The text has been amended to match the evidence statement for this evidence. (Refer to the full guideline, section 5.18.3, important outcomes). It now reads, “4.8g mesalazine (MMX) has been excluded from the NMA as it did not demonstrate a dose effect in the clinical review and was thought to have the same effect as 2.4g mesalazine (MMX) at a greater cost. There was no difference in the risk of adverse events.”</p>

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						Efficacy has been commented on in order number (row) 4 above.	
SH	Shire Pharmaceuticals	6	Appendix A to E	9		<p>Appendix A Section 2.1 f page 9/85 Under Need for guidance, Epidemiology.</p> <p>“Moreover the degree of colonic inflammation in ulcerative colitis 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”</p> <p>Does the key research recommendation on Page 50 Full Nice guidance Section 4.4 Number 4 line 10-12 regarding a comparison of “..regular maintenance treatment against no regular treatment..” undermine the above thinking in the appendices.</p> <p>Other research recommendations could involve the clinical and cost effectiveness of monitoring patients with faecal calprotectin; the optimal length of time for high dose mesalazine use in getting mild to moderate patients into remission: Treatment strategies for patients with distal disease who are intolerant or refractory to topical therapy whilst avoiding steroids.</p>	<p>Thank you for your comment. The GDG does not agree with this interpretation. The question of no regular maintenance is an important clinical question and in the other considerations section of the Recommendations and link to evidence for maintenance therapy (see section 7.25) the GDG discussions are summarised.</p> <p>‘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.</p> <p>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</p>

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							<p>such a recommendation.'</p> <p>As a result of these deliberations the GDG decided it was important to have a research recommendation exploring this issue.</p> <p>Thank you for the suggestion of other research recommendations.</p>
SH	Tillotts Pharma UK Ltd	1	Full	General		Mesren has now been rebranded as Octasa 400 and at the time of publication of these guidelines will no longer be available.	<p>Thank you for your comment. The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the trade name:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence The BNF states that: The delivery characteristics of oral mesalazine</p>

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							<p>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 they are named in the studies. We are aware that the mesalazines can change brand names, for example Mesren was rebranded as Octasa 400 in December 2012.</p> <p>Section 5.40 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates 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>Other considerations '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</p>

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							<p>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 identifying a preferred mesalazine.'</p> <p>Section 7.25 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: sulphasalazine, balsalazide, olsalazine and mesalazine (the brand names of the mesalazines in the published papers were Asacol and Pentasa). Mezavant XL, Ipocol Mesren, Octasa were not named in the papers.</p> <p>Other considerations '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 identifying a preferred mesalazine.'</p>
SH	Tillotts Pharma UK Ltd	2	Full	50	13	May help to add after "Mesren" (now rebranded as Octasa 400mg) regarding	Thank you for your comment. This research recommendation has been changed to the

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						the point above?	development of a risk tool for assessing surgery.
SH	Tillotts Pharma UK Ltd	3	Full	General		<p>Several sections (detailed below in lines 4 - 8)) make reference to Mesren and Octasa not being included in the analyses due to "lack of relevant clinical data". Several references presented under "Asacol" are indeed utilising Tillotts UK formulation (marketed as Mesren in the UK, but Asacol in other countries). Tillotts developed and brought "Asacol" to the UK market in 1985. However the tradename is currently owned, in the UK only, by Warner Chilcott. Tillotts still market Asacol (know as Mesren and Octasa in the UK) as Asacol in 55 countries as well as marketing the same product as Lixacol (Spain), Asacolon (Ireland) and Fivasa (France) References quoted such as Ito et al (references 101 and 102) utilise Tillotts formulation (mesren) but named and marketed as Asacol in Japan. In addition older references such as Riley et al - ref178 use Tillotts formulation being manufactured today to the same spec and sold in the UK as Mesren. Ref 203 – Sninsky et al also utilises Tillotts preparation as does Schroeder et al reference 196</p>	<p>Thank you for your comment. The following text has been added in the following sections of the guideline to clarify that the mesalazines named in the reviews are those named in the studies and to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence 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</p>

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							<p>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 they are 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.</p> <p>Section 5.40 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: 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>Other considerations '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</p>

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SH	Tillotts Pharma UK Ltd	4	Full	144	9 -10	See comment above regarding Tillotts data used and referred in the literature as "Asacol"	Thank you for your comment. The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company

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							<p>owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence 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</p>

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SH	Tillotts Pharma UK Ltd	5	Full	159	6	See comment above regarding Tillotts data used and referred in the literature as "Asacol"	<p>Thank you for your comment. The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission,

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							<p>clinical evidence for oral aminosalicylates</p> <ul style="list-style-type: none"> Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence 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.</p> <p>Section 5.40 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: sulphasalazine, balsalazide, olsalazine and mesalazine (The brand names of the mesalazines in the published papers were</p>

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							<p>Asacol, Pentasa, Mezavant XL and Ipocol). Mesren or Octasa were not named in the papers.</p> <p>Other considerations '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 identifying a preferred mesalazine.'</p> <p>Section 7.25 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: sulphasalazine, balsalazide, olsalazine and mesalazine (The brand names of the mesalazines in the published papers were Asacol and Pentasa). Mezavant XL, Ipocol Mesren, Octasa were not named in the papers.</p> <p>Other considerations 'The GDG are aware that the mesalazines can be called different brand names in different countries (for example, Mesren is</p>

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SH	Tillotts Pharma UK Ltd	6	Full	159	Last line	See comment above regarding Tillotts data used and referred in the literature as "Asacol"	<p>Thank you for your comment. The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence The BNF states that: The delivery characteristics of oral mesalazine</p>

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							<p>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.</p> <p>Section 5.40 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: 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>Other considerations '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</p>

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SH	Tillotts Pharma	7	Full	226	12	See comment above regarding Tillotts	Thank you for your comment. The following

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	UK Ltd					data used and referred in the literature as "Asacol"	<p>text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence 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</p>

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SH	Tillotts Pharma UK Ltd	8	Full	237	12	See comment above regarding Tillotts data used and referred in the literature as "Asacol"	<p>Thank you for your comment. The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission,

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							<p>quality of evidence and other considerations boxes in the Recommendations and link to evidence</p> <ul style="list-style-type: none"> • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence 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.</p> <p>Section 5.40 Quality of evidence</p>

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							<p>The GDG noted that evidence was identified on the following oral aminosalicylates: 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>Other considerations '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 identifying a preferred mesalazine.'</p> <p>Section 7.25 Quality of evidence The GDG noted that evidence about the following oral aminosalicylates 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, Octasa were not named in the papers.</p>

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SH	Tillotts Pharma UK Ltd	9	Full	93	Table 33	It is difficult to establish if these are Warner Chilcott Asacol studies. Warner Chilcott only supply Asacol in the UK + USA and Tillotts elsewhere (55 countries). Some references (e.g. those identified above) relate to Tillotts Asacol sold in other countries. Although Tillotts believes the results from the Tillotts studies are reflective of Warner Chilcotts studies (and vice versa), to group all studies under "Asacol" may be misleading if it is expressed that there is no data for Mesren or Octasa.	Thank you for your comment. The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename: <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence

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							stated as 'may not be interchangeable' in the BNF and in identifying a preferred mesalazine.'
SH	Tillotts Pharma UK Ltd	10	Full	106	Table 43	If the Ito et al studies are referenced here this is relevant to Tillotts Asacol (i.e. Mesren)	<p>Thank you for your comment. The GDG acknowledge that the Ito et al study named Asacol and Pentasa but that in the UK Asacol has been branded as Mesren and now Octasa.</p> <p>The following text has been added to the following sections of the guideline to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence • Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates • Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence The BNF states that: The delivery characteristics of oral mesalazine preparations may vary; these preparations</p>

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							<p>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 identifying a preferred mesalazine.'</p> <p>Section 7.25 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: sulphasalazine, balsalazide, olsalazine and mesalazine (the brand names of the mesalazines in the published papers were Asacol and Pentasa). Mezavant XL, Ipocol Mesren, Octasa were not named in the papers.</p> <p>Other considerations '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 identifying a preferred mesalazine.'</p>
SH	Tillotts Pharma UK Ltd	11	Full	111		A question as to which Asacol was used?	Thank you for your comment. The studies included in this section name the oral

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							mesalazine evaluated as Asacol. No other details on which Asacol is given. The references are Schroeder1987; Migilio1990; ITO2010A; Sandborn2009A; Hanauer2005; Hanauer2007; Irvine2008.
SH	Tillotts Pharma UK Ltd	12	Full	General		3 new references are attached for consideration and inclusion. All relate to Octasa or Tillotts Asacol 400mg (Mesren)	Thank you for your comment. Conference abstracts are searched for in the core databases and only included in reviews when there are no other full publications available (see chapter 2). The Feagan et al abstract is not indexed in the core databases searched. In addition Yoshimra et al, and Ahulwala et al do not meet the inclusion criteria stated in the review protocol (see Appendix C). Yoshimra et al is not a randomised trial and Ahulwala et al does not report the required outcomes.
SH	Tillotts Pharma UK Ltd	13	Appendix K	6	Table 4	May wish to add price of Octasa 800 which is £95 per 180 and Mesren (Octasa 400) which is £19.50 for 90.	Thank you for your comment. The drugs listed are those that have been addressed in the guideline. The reviews in this guideline name the mesalazine as it is named in the studies. In the cost effectiveness model, individual mesalazines are not compared therefore an average cost of named mesalazines (from the clinical review) was used. A sensitivity analysis was conducted looking at the effect of drug costs on the model results. The GDG noted that the use of cheaper mesalazines would make the treatment strategies more cost effective.

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SH	Tillotts Pharma UK Ltd	14	Appendix K	19	Table 24	Could add Mesren at £19.50 per 90. Note Asacol, dose for dose, is 50% more expensive and Mesren (Octasa 400) and may effect your cost effectiveness model? Attached is data showing the average prescription price for UK mesalazines.	<p>Thank you for your comment. The drugs listed are those that have been addressed in the guideline.</p> <p>The reviews in this guideline name the mesalazine as it is named in the studies. In the cost effectiveness model, individual mesalazines are not compared therefore an average cost of named mesalazines (from the clinical review) was used. A sensitivity analysis was conducted looking at the effect of drug costs on the model results. The GDG noted that the use of cheaper</p>





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SH	Tillotts Pharma UK Ltd	15	Appendix K	19	Table 25	Could add Octasa 800 at £95 per 180 (which is licensed to 4.8g/d). Note that Asacol 400 is not licensed at a dose above 2.4g/day only the 800 mg is licensed at high dose – 4.8g/d.	Thank you for your comments. The costing for Asacol 400 has been amended to reflect its licence.
SH	Tillotts Pharma UK Ltd	16	NICE	General		Is it worth mentioning 2012 ECCO guidelines – recommendation (page 12 of guidelines)	Thank you for your comment. We are aware of the ECCO 2012 guidelines. NICE guidelines do not cross refer to non-NICE clinical guidelines.

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						<p>follow up. Proprietary prescribing of mesalazine has recommended,¹⁶⁰ but for active UC the choice of cannot be made on the grounds of efficacy alone. The of delivery, dose frequency, cost and availability are relevant factors in the choice.</p> <p>Page 12 of 0.79 (95% CI 0.73–0.85; NNT=6).²⁰ Available data c suggest a difference in efficacy between any of the preparations for active UC. As discussed in Section 1.2.2,</p> <p>Page 18 of ECCO 2012 guidelines regarding maintenance therapy. any of these studies. Taken together, in conjunction the likely improvement in patient convenience and a ence to treatment, this make once daily administrat 5ASA compounds the first choice in maintenance ther patients with UC.</p>	
SH	Tillotts Pharma UK Ltd	17	Full	General		<p>Warner Chilcott currently own the trade name "Asacol" in the UK and Tillotts own the rights to the Asacol trade name in 55 other countries. Tillotts used to own the rights to the name in the UK but this has since been sold on. As such some of the clinical trials, although they may state "Asacol", utilise Tillotts 5ASA (Mesren/Octasa). Although we believe the data is all much of a muchness and one clinical trial is reflective of the others products we felt we should point this out as several sections state that there is no information on Mesren/Octasa.</p> <p>In addition I have attached some</p>	<p>Thank you for your comment. The following text has been added in the following sections of the guideline to clarify that the mesalazines named in the reviews are those named in the studies and to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> • Section 5.15 induction of remission, clinical evidence for oral aminosalicylates • Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence

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						<p>additional references (abstracts) for consideration and relate to comments made in our stakeholders comments document. Again although these abstracts state Asacol they are Tillotts Asacol – know as Mesren in the UK. Note: Mesren is no longer available under that tradename now in the UK, and is called Octasa 400.</p> <div>  wave data screen shot.pptx  Poster_Octasa_A3.pdf  UEGW12-1757-preview-1.pdf  Ahluwalia1992;102.pdf </div>	<ul style="list-style-type: none"> Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence <p>Sections 5.15 and 7.11. Clinical evidence 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 they are 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.</p> <p>Section 5.40 Quality of evidence The GDG noted that evidence was identified on the following oral aminosalicylates: sulphasalazine, balsalazide, olsalazine and</p>

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							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 identifying a preferred mesalazine.'
SH	UKCPA	1	NICE	15	17	Under section 1.16 "offer a high induction dose of an oral aminosalicylate". I think that the definition of high dose should be given. I note that the definition is given in the full guideline but I think this is important that the same info is stated in the NICE guideline otherwise the recommendation is less clear/useful.	Thank you for your comment. NICE guidelines do not usually give doses in recommendations. Readers are expected to refer to the summary of product characteristics (SPC) for details of dosages. SPCs can be found in the Electronic Medicines Compendium (refer to section 9.3.6.2 NICE guidelines manual 2012). As you have noted the GDG have outlined these doses in the other considerations section of the Evidence and Link to Recommendation for the Induction of remission (see section 5.40).
SH	UKCPA	2	NICE	21	6	Section 1.3.2 "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." Again, I think it is important that a definition of low dose is given. I note that	Thank you for your comment. NICE guidelines do not usually give doses in recommendations. Readers are expected to refer to the summary of product characteristics (SPC) for details of dosages. SPCs can be found in the Electronic Medicines Compendium (refer to section 9.3.6.2 NICE guidelines manual 2012).The GDG have outlined these doses in the other

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						this definition is given in the full guideline but think that this is an important point and warrants including in the NICE guideline for clarity, especially as with 4.8g being considered "high dose", there is the risk of now considering 2.4g as "low dose" when in fact the definition given is 1.2g for asacol type preparations.	considerations section of the Evidence and Link to Recommendation for the maintenance of remission (see section 7.25).
SH	Warner Chilcott UK Ltd	1	Full	General		<p>Thank you for the opportunity to comment on the draft guideline. Whilst we agree in general with the guideline recommendations and support these, there are two recommendations which we consider require revision in order to provide clear and robust guidance to clinicians and patients to be consistent with the guideline process and the evidence reviewed.</p> <p>Our two main concerns relate to the:</p> <ul style="list-style-type: none"> The recommendation: <i>'To maintain remission in adults after mild to moderate inflammatory exacerbation of left-sided or extensive ulcerative colitis, offer a low maintenance dose of an oral aminosalicylate. When deciding on which oral aminosalicylate to use, take into account the person's preferences, side effects and costs'</i> (Full guideline recommendation 27, 	<p>Thank you for your comment. In response to your first concern, based on the evidence identified the efficacy of the different mesalazines was compared and no one mesalazine was identified as clinically more effective. Section 5.40 summarises the findings found in chapter 5 exploring this issue.</p> <p>We have also noted that the mesalazines can be rebranded. The following text has been added in the following sections of the guideline to clarify that the mesalazines named in the reviews are those named in the studies and to highlight that the brand names of some of the mesalazines may change according to which company owns the tradename:</p> <ul style="list-style-type: none"> Section 5.15 induction of remission, clinical evidence for oral aminosalicylates Section 5.40 induction of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence

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						<p>page 47) This recommendation omits reference to the fact that mesalazine preparations are not interchangeable. Oral aminosalicylate preparations are formulated to target specific parts of the bowel and should never be interchanged because they have different indications and delivery characteristics.</p> <p>In addition, we consider that the choice of aminosalicylate needs to take into account the efficacy of the product first and foremost.</p> <ul style="list-style-type: none"> The recommendation: <i>'Consider a once-daily dosing regimen for oral aminosalicylates 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'</i> (Full guideline recommendation 29, page 48) This recommendation appears to be based on the views of the Guideline Development Group (GDG) and is not supported by the evidence considered. 	<ul style="list-style-type: none"> Section 7.11 maintenance of remission, clinical evidence for oral aminosalicylates Section 7.25 maintenance of remission, quality of evidence and other considerations boxes in the Recommendations and link to evidence. <p>In response to your second concern, the rationale for the GDG decision about making a recommendation to consider the use of once daily dosing is outlined in section 7.25, 'trade off between clinical benefits and harms' under the heading regime. The GDG acknowledge the evidence was of very low to low quality. The evidence showed there is no clinical difference between taking a once a day dose of an oral ASAs compared to conventional dosing (more than once a day) although the side effects may be greater with once daily dosing. 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 and reflected this in recommendation 29 (now 32). The GDG noted that if people did experience side effects with once daily dosing the dose should be split across the day.</p>

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						Further details on each of these and additional points are provided below.	The recommendation is 'to consider' to reflect the strength of the evidence.
SH	Warner Chilcott UK Ltd	2	Full	44	16 to 20	<p>We support the recommendation to offer a high induction dose of an oral aminosalicylate to induce remission in adults with a mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis (NICE full guideline recommendation 6). High dose oral ASAs alone (without the need for topical therapy) have, as supported by the evidence considered by the GDG, been proven to be clinically and cost effective in inducing remission.</p> <p>In order to ensure clinicians are provided with details of the high dose oral aminosalicylates considered by the GDG we recommend a footnote is added listing these and suggest the draft recommendation is revised as follows:</p> <p><i>'To induce remission in adults with a mild moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis:</i></p> <ul style="list-style-type: none"> • <i>offer a high induction dose¹ of an</i> 	<p>Thank you for your comment. NICE guidelines do not usually give doses in recommendations. Readers are expected to refer to the summary of product characteristics (SPC) for details of dosages. SPCs can be found in the Electronic Medicines Compendium (refer to section 9.3.6.2 NICE guidelines manual 2012).The GDG have outlined these doses in the other considerations section of the Evidence and Link to Recommendation for the Induction of remission (see section 5.40).</p>

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						<p><i>oral aminosaliclylate</i></p> <ul style="list-style-type: none"> <i>consider adding a topical aminosaclylate or oral beclometasone dipropionate, taking into account the person's preference'</i> <p>1. <u>Mesalazine >2.4g, sulphasalazine >6g, balsalazide ≥6.75g, olsalazine ≥1.5g</u></p>	
SH	Warner Chilcott UK Ltd	3	Full	47 and 48	35 to 36 and 1 to 3	<p><u>Omission of a statement specifying that mesalazine preparations are not interchangeable</u></p> <p>The draft recommendation 27 does not specify that aminosaliclylates are not interchangeable despite this being recognised in the main body of the full guideline which states (page 86, lines 34 and 35) <i>'The BNF states that: The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable'</i>.</p> <p>In order to ensure clinicians and patients are fully informed of the fact that mesalazine preparations are not interchangeable, it is essential that the final recommendation includes an appropriate statement and we would like to propose the addition of the following</p>	<p>There are several references to the BNF statement that mesalazine preparations are not interchangeable. Refer to sections 5.15, 5.40 (trade off between clinical benefits and harms and other considerations sections) and 7.11.</p> <p>The evidence reviews for the maintenance of remission included dose, formulation, regime, mode of delivery and interclass comparisons where possible. The recommendations are based on this evidence and the economic model. The rationale is summarised throughout the Recommendations and link to evidence box (section, 7.11). No clinically important differences were found between the mesalazine preparations, as such the GDG felt it would be inappropriate to add the suggested text.</p> <p>Recommendations 1.3.2 (now 1.4.2) and</p>

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						<p>text:</p> <p><i>'The delivery characteristics of oral mesalazine preparations may vary. These preparations should not be interchanged and should always be prescribed by brand.'</i></p> <p>In addition, following review of the comments submitted at the scoping stage inclusion of our recommended additional text below will allay the concerns of patient groups (including Crohn's and Colitis UK) with regard to the effect on patients of being switched medication solely on cost grounds and without consideration of the BNF guidance.</p> <p>To fully reflect the medicines considered by the GDG, we also recommend evidence of proven efficacy is added to the criteria to be taken into account when selecting an oral aminosalicylate as well as side effects and costs. We also recommend that in order to highlight the importance of proven efficacy in the selection process this is listed first. We also suggest that consideration of side effects is listed before the person's preference as both efficacy and side effects are likely to inform a person's preference.</p>	<p>1.3.3 (now 1.4.3) indicate that when considering which oral aminosalicylate to use the person's preferences and side effects should be taken into account. It is imperative that costs are considered.</p> <p>In addition recommendation 1.1.2 states the importance of discussing side effects of drug treatment and refers readers to the NICE clinical guideline 76, Medicines adherence.</p> <p>The GDG agree that the decision to decide which medical treatment to use is multifaceted requiring the careful consideration of many factors, they are confident this is reflected in the recommendations and throughout the guideline.</p> <p>The recommendations are based on the evidence reviewed and the GDG have noted in the 'trade off between clinical benefits and harms' section of the Recommendations and link to evidence box for the maintenance of remission (section 7.25) that all the treatments are better than placebo and that all the confidence intervals overlapped. This led to the GDG to conclude there is insufficient evidence to be confident of one's treatment superiority over the other with reference to efficacy. Adding</p>

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						<p>In order to ensure clinicians are aware of the low dose aminosalicylate licensed preparations available we also recommend including a reference to the BNF.</p> <p>We suggest the draft recommendation is revised as follows:</p> <p><i>'To maintain remission in adults after 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 <u>evidence of proven efficacy</u>, the person's preferences, side effects, <u>the person's preferences</u> and cost. When selecting a low dose aminosalicylate preparation it is important to refer to the BNF for currently available licensed preparations. The delivery characteristics of oral mesalazine preparations may vary. These preparations should not be interchanged and should always be prescribed by brand.'</i></p>	<p>efficacy into the recommendation is unnecessary. The recommendation indicates oral aminosalicylate are effective but there is no strong evidence to suggest that one aminosalicylate is better than the other.</p> <p>The GDG are happy with the wording and the order of the factors listed in the recommendations.</p>
SH	Warner Chilcott UK Ltd	4	Full	48	10 to 13	<p><u>Once daily dosing</u></p> <p>We are concerned that the statement 'once-daily dosing can be more effective but may result in more side effects' is</p>	<p>Thank you for your comment. The rationale for the GDG decision about making a recommendation to consider the use of once daily dosing is outlined in section 7.25, 'trade off between clinical benefits and</p>

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						<p>based on the views of the GDG rather than published evidence particularly as the views of the GDG are not supported by the evidence. This is inappropriate and contrary to the statement on page 17 that clinical guidelines should be based '<i>on the best available research evidence</i>'.</p> <p>It is contradictory that the draft recommendation states that once daily dosing can be more effective when, based on the evidence considered, page 237 of the full guideline states '<i>there is no clinical difference between taking a once daily oral ASA compared to conventional dosing (more than once a day)</i>'.</p> <p>The fact that the draft recommendation is solely based on the views of the GDG is further supported by the following statements:</p> <ul style="list-style-type: none"> • Pages 237 – 238 '<i>The GDG recognised that some people would prefer once daily dosing regimens but acknowledged the evidence was limited and that the benefits needed to outweigh the risks of possible additional adverse and serious adverse events</i>'. We would also suggest that this statement is misleading as we are unable to find any 	<p>harms' under the heading regime. The GDG acknowledge the evidence was of very low to low quality. There is no clinical difference between taking a once a day dose of an oral ASAs compared to conventional dosing (more than once a day) although the side effects may be greater with once daily dosing. 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 and reflected this in recommendation 29 (now 32). The GDG noted that if people did experience side effects with once daily dosing the dose should be split across the day.</p> <p>The Ford et al 2011 is listed in the excluded studies (Appendix F). The Ford et al had different outcome definitions than those stated in the guideline protocol. The studies in the Ford et al review have been included where they met the protocol inclusion criteria.</p> <p>The recommendations are based on the evidence reviewed and the GDG have noted in the 'trade off between clinical benefits and harms' section of the</p>

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						<p>evidence within the full guideline which supports patient preference for a once daily dose.</p> <ul style="list-style-type: none"> Page 240 '<i>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 adherence.</i>' We are concerned that such a statement, which is again not supported by any evidence, is also by the use of terms such as '<i>felt</i>' and '<i>may</i>' entirely subjective. <p>We would like to draw to the attention of the GDG that its clinical literature search omitted the 2011 publication reporting the results of a systematic review and meta-analysis of once-daily dosing vs. a conventional dosing schedule of mesalazine and relapse of quiescent ulcerative colitis (Ford <i>et al.</i> 2011). This review and analysis clearly demonstrate that once-daily dosing with mesalazine is as effective as conventional dosing regimens and highlights that there is no evidence that adherence with once daily dosing is better compared with conventional dosing or associated with an</p>	<p>Recommendations and link to evidence box for the maintenance of remission (section 7.25) that all the treatments are better than placebo and that all the confidence intervals overlapped. This led to the GDG to conclude there is insufficient evidence to be confident of one's treatment superiority over the other with reference to efficacy. Adding efficacy into the recommendation is unnecessary. The recommendation indicates oral aminosalicylate are effective but there is no strong evidence to suggest that one aminosalicylate is better than the other.</p> <p>The GDG are happy with the wording and the order of the factors listed in the recommendations.</p> <p>The GDG agree with the CG76 recommendation that dosing regimes (initial or when changing regimes) should be tailored to the needs of individual patients. For some people on maintenance aminosalicylates this may be a preference to take one tablet a day and may improve adherence. This is reflected in the wording of recommendation 29 (now 32) 'Consider a once-daily dosing regimen for oral aminosalicylates 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</p>

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						<p>increase in adverse events.</p> <p>We would also highlight that during development of the the NICE clinical guideline 76: <i>Medicines adherence - Involving patients in decisions about prescribed medicines and supporting adherence</i> the question 'Does change in dosing regime affect adherence?' was fully evaluated and no evidence to support once-daily dosing over other regimens identified (see full guideline section 8.5). The GDG considered '<i>that the evidence does not support that developing once-daily formulations and combined pills will necessarily improve adherence</i>' and recommended that '<i>changes to dosing regime need to be tailored to needs of individual patients</i>' (CG 76, Full guideline, section 8.5.1, pages 209 – 210).</p> <p>In order to ensure clinicians and patients are provided with a recommendation which is evidence based while retaining patient choice we recommend that the draft recommendation is revised as follows:</p> <p><u>'Offer an oral aminosalicylate for maintaining remission. Consider a once-daily dosing regimen for oral aminosalicylates for maintaining remission</u></p>	<p>in more side effects.'</p>

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						<p><i>Take into account <u>evidence of proven efficacy</u>, person's preference, side effects, the <u>person's preferences</u> and cost and explain that once-daily dosing can be more effective, but may result in more side-effects'</i></p> <p>We have included 'evidence of proven efficacy' with the factors to be taken into account when selecting an oral aminosalicylate in order to ensure both patients and clinicians take into account efficacy as well as side effects and costs. We also suggest that consideration of side effects is listed before the person's preference as both efficacy and side effects are likely to inform a person's preference.</p> <p><u>Reference</u> Ford AC, Khan KJ, Sandborn WJ <i>et al</i>. Once-daily dosing vs. conventional dosing schedule of mesalamine and relapse of quiescent ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol 2011. doi:10.1038/ajg.2011.296</p>	
SH	Warner Chilcott UK Ltd	5	Full	87	4	MMX is cited on page 87 – this is inconsistent with how all other treatments in the same sentences are listed with these referred to by brand name. For the purposes of consistency and in order to	Thank you for your comment. We have made this change.

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						define which brand is being referred to (there are several different MMX preparations such as low weight heparin MMX and budesonide MMX) MMX should be replaced with the appropriate brand name, Mezavant XL.	
SH	Warner Chilcott UK Ltd	6	Full	95		<p><u>Table documenting ASCEND I and ASCEND II</u></p> <p>Details on the severity of disease for both studies are incorrect. ASCEND I evaluated patients with mild and moderate ulcerative colitis and ASCEND II patients with moderate ulcerative colitis.</p>	Thank you for your comment. We have made this change.
SH	Warner Chilcott UK Ltd	7	Full	95	10-13	<p>The below statement relating to the SANDBORN2009A study (ASCEND III) is inaccurate and does not take account the evaluation technique used in the study compared with that used in ASCEND I and II.</p> <p><i>'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'</i></p>	<p>Thank you for your comment. The Sandborn study reports results that favour the lower dose for clinical and endoscopic remission (RR 1.93).</p> <p>This statement refers to the subgroup analysis investigating the heterogeneity when the ASCEND trials are combined. The GDG agreed on the areas for subgroup analysis if heterogeneity was found prior to the review being undertaken and are set out in the protocols (See Appendix C). The GDG did not identify evaluation technique as a potential reason for heterogeneity in the protocol and as such it was not explored in the subgroup analysis. The process for undertaking subgroup analysis is detailed in the methods chapter</p>

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						The SANDBORN2009 study (ASCEND III) included a different evaluation technique for assessing sigmoidoscopic improvement and mucosal healing compared with ASCEND I and ASCEND II. In ASCEND III a novel,)unvalidated technique, the contact friability test (CFT) was used. However, the technique may have had the effect of overestimating friability (and thus underestimating sigmoidoscopy improvement) compared with the usual technique of assessing contact friability caused by normal passage of the flexible sigmoidoscope. For this reason, rates of sigmoidoscopy improvement reported in the ASCEND III trial cannot be compared with those reported in other ulcerative colitis studies including ASCEND I and II. The differences in efficacy reported by the GDG are considered to be due to the difference in the evaluation technique used.	of the main guideline (see chapter 2; section 3.3.6).
SH	Warner Chilcott UK Ltd	8	Full	239		Other considerations section The low maintenance doses as defined by the GDG require a footnote clarifying that not all available licensed preparations are listed. While Asacol 1.2g is listed Asacol MR preparations are not. Asacol 400mg MR tablets are licensed for maintenance of remission at 1.2 to 2.4 g/day and Asacol	Thank you for your comment. A footnote has been added in the recommendations noting not all the mesalazines are licensed for once daily dosing.

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						Please insert each new comment in a new row.	Please respond to each comment
						800mg MR tablets at 1.6g-2.4 g/day.	

These organisations were approached but did not respond:

AAH Pharmaceuticals
 Action Cancer
 Aintree University Hospital NHS Foundation Trust
 Alder Hey Children's NHS Foundation Trust
 Allocate Software PLC
 Association of Anaesthetists of Great Britain and Ireland
 Association of British Healthcare Industries
 Association of Clinical Pathologists
 Association of Coloproctology of Great Britain and Ireland
 Association of Surgeons in Primary Care
 B. Braun Medical Ltd
 Barnsley Hospital NHS Foundation Trust
 Bladder and Bowel Foundation
 Bonpharma Ltd
 Boots
 Bowel Cancer UK
 Bradford District Care Trust
 Bridgewater CHC
 British Acupuncture Council
 British Association of Plastic, Reconstructive and Aesthetic Surgeons)
 British Dietetic Association
 British Healthcare Trades Association
 British Infection Association
 British Medical Association
 British Medical Journal
 British National Formulary
 British Nuclear Cardiology Society

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British Psychological Society
British Society for Immunology
British Society for Paediatric Endocrinology and Diabetes
British Society of Paediatric Gastroenterology Hepatology and Nutrition
British Specialist Nutrition Association
BUPA Foundation
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Capsulation PPS
Capsulation PPS
Care Quality Commission (CQC)
Clarity Informatics Ltd
CM&D Pharma Limited
Covidien Ltd.
Crohn's in Childhood Research Association
Croydon Health Services NHS Trust
Deltex Medical
Department for Communities and Local Government
Department of Health, Social Services and Public Safety Northern Ireland
DO NOT USE (Disbanded) Primary Sclerosing Cholangitis Support
East and North Hertfordshire NHS Trust
Expert Patients Programme CIC
Faculty of Occupational Medicine
Five Boroughs Partnership NHS Trust
gastroenterology specialist group
George Eliot Hospital NHS Trust
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINK
Great Western Hospitals NHS Foundation Trust
Halton & St. Helens Primary Care Trust
Hammersmith and Fulham Primary Care Trust
Hayward Medical Communications
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Hindu Council UK

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Hockley Medical Practice
Hospira UK Limited
Humber NHS Foundation Trust
IA
Independent Healthcare Advisory Services
Institute of Biomedical Science
Johnson & Johnson
KCARE
KCI Medical Ltd
Kidney Alliance
L.IN.C.Medical
Lancashire Care NHS Foundation Trust
Leeds Community Healthcare NHS Trust
Liverpool Primary Care Trust
Luton and Dunstable Hospital NHS Trust
McMDC Ltd
Medicines and Healthcare products Regulatory Agency
Ministry of Defence
National Association of Primary Care
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Diabetes Nurse Consultant Group
National Institute for Health Research Health Technology Assessment Programme
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS County Durham and Darlington
NHS England
NHS Hertfordshire
NHS Plus
NHS Sheffield
NHS Warwickshire Primary Care Trust

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NICE technical lead
Norgine Limited
North and East London Commissioning Support Unit
North Tees and Hartlepool NHS Foundation Trust
Nottingham City Council
Nottingham City Hospital
Nottingham University Hospitals NHS Trust
Nutrition and Diet Resources UK
Oxford Health NHS Foundation Trust
Parenteral and Enteral Nutrition Group
Pelvic Pain Support Network
Pfizer
Pharmametrics GmbH
Primary Care Pharmacists Association
Primary Care Society for Gastroenterology
Primary Care Society for Gastroenterology
Public Health Wales NHS Trust
RioMed Ltd.
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Paediatrics and Child Health, Gastroenterology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Psychiatrists
Royal College of Surgeons of Edinburgh
Royal College of Surgeons of England
Royal Free London NHS Foundation Trust
Royal National Institute of Blind People
Royal Pharmaceutical Society
Royal Society of Medicine
Sandoz Ltd
Scottish Intercollegiate Guidelines Network
Sheffield Childrens Hospital
Sheffield Teaching Hospitals NHS Foundation Trust

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SNDRI
Social Care Institute for Excellence
Society and College of Radiographers
Society for Acute Medicine
Solvay
South Asian Health Foundation
South East Coast Ambulance Service
South London & Maudsley NHS Trust
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St Mary's Hospital
Takeda UK Ltd
Teva UK
The Association for Clinical Biochemistry & Laboratory Medicine
The British In Vitro Diagnostics Association
The Rotherham NHS Foundation Trust
UCB Pharma Ltd
University Hospital Birmingham NHS Foundation Trust
University Hospitals Birmingham
Vifor Pharma UK Ltd
ViroPharma Ltd
Vitaline Pharmaceuticals
Walsall Local Involvement Network
Welsh Government
Western Cheshire Primary Care Trust
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
Wirral University Teaching Hospital NHS Foundation Trust
York Hospitals NHS Foundation Trust

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