Crohn's Disease Management (update CG152)

Consultation on draft guideline - Stakeholder comments table
18/12/2018 to 22/12/2019

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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AbbVie	Guideline	13	4-6	We are concerned that this recommendation may cause clinicians to be unclear whether biologics can be used in patients who post-surgery are no longer in remission. To clarify the situation the following wording should be added to this recommendation "For patients who cease to be in remission post-surgery biologics can be used in line with the recommendations outlined in Sections 1.2.12-1.2.22 of this guideline".	Thank you for your comment. The recommendations in 1.4 states that they are to maintain remission in people with ileocolonic Crohn's disease who have had complete macroscopic resection. For people whose disease is no longer in remission after surgery, refer to the appropriate section of the guideline (1.2.1 to 1.2.20).
British Association for Behavioural and Cognitive Psychotherapies (BABCP)	Guideline	17	25 onwards	In the discussion of CD in the section: context, it is noted that it is a lifelong disease that can affect a person's social and psychological wellbeing, particularly if poorly controlled. The guideline does not include any recommendation for the assessment or measurement of psychological wellbeing or the consideration of psychological treatment for people with CD who are identified as experiencing persistent disturbance to mood post-surgery or prior to surgery. Ulcerative Colitis (UC) and Crohn's disease (CD) pose numerous challenges for both physical and psychosocial functioning. Adults with UC & CD experience unpleasant and unpredictable symptoms and aggressive treatment regimes. In addition they face psychosocial consequences including disruptions to their life goals, employment, and social and leisure activities (Kemp et al 2012). Psychosocial difficulties are common in UC and CD when compared to both non-clinical (Kovac et al, 2007) and other chronic disease populations (Fillpovic et al, 2007). The empirical evidence demonstrates the life time prevalence rates of anxiety and depression to be 35.8% for people with UC and CD (Walker et al, 2008). The presence of mood disturbance has been established as being an independent risk factor for earlier and more active disease (Mittermaier et al, 2004, Graff et al, 2006, Mikocka –Walus et al, 2016) and is associated with poorer clinical outcome and increased healthcare utilization in patients with UC and CD (Mickocka-Walus et al, 2012). Although disease related factors such as remission status, frequency of relapse, pain severity, and extra intestinal manifestations have been linked to emotional distress and poor quality of life in UC & CD, evidence suggests that psychological factors have a comparable influence (Jordan et al, 2016). A recent systematic review found that emotion focused coping strategies, extreme perceptions of the illness and of being stressed were significantly associated with worse mental health outcomes, and this was maintained when controlling for the influence of clinical factors (Jordan et al, 2016). Disease activity and psychological functioning are likely to be interrelated	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. Quality of life was included in the protocol for this guideline update as an outcome, but there was limited evidence on this outcome. Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed your comment on to the surveillance team for consideration in future updates.

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				and bidirectional.	
British Association for Behavioural and Cognitive Psychotherapies (BABCP)	Guideline	12	16	Post-surgery remission recommendations include no reference to psychological intervention.Qualitative studies exploring the burden of living with IBD from the patients' perspective have described symptoms of anxiety as linked to a fear of embarrassing symptoms occurring in public. This has been reported to lead to range of behavioural responses intended to minimise the probability of this occurring such as always knowing the whereabouts of toilets. Low mood has been liked to a perceived lack of understanding of IBD from others and to feeling stigmatised which has been reported to lead to behavioural withdrawal (Kemp et al, 2012, Jordan et al, 2018). Cognitive and behavioural responses are potentially modifiable factors which it is possible to address in a psychological intervention and people with UC and CD have been found to state a desire for psychological support. The findings of qualitative studies suggest a strong preference for this to be delivered by a compassionate practitioner who can draw on specialised knowledge of the key symptoms of IBD and their impact on functioning and mental health, with a focus on building coping strategies (Jordan et al, 2018). A meta-analysis conducted by Timmer and colleagues (2011) concluded that there was no evidence that psychological interventions in general enhance emotional states, HRQOL and disease activity for adults with IBD. However, there are limitations to this review. The authors combined stress management, psychodynamic psychotherapy and cognitive behaviour therapy (CBT) studies as "psychotherapy" in the meta–analysis, therefore any differential efficacy between these theoretically distinct approaches could not be evaluated. When considered independently, a more recent review found promising evidence that CBT improved mental health in patients with IBD, both immediately following the intervention and at 6 months follow up (Knowles et al, 2013). In addition both reviews have included studies where the majority of participants have sub clinical levels of anxiety and depression which is likely to have reduced treatment effects.	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. Quality of life was included in the protocol for this guideline update as an outcome, but there was limited evidence on this outcome. Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed your comment on to the surveillance team for consideration in future updates.
British Association for Behavioural and Cognitive Psychotherapies (BABCP)	Guideline	12	16 cont.	Several studies carried out since the above mentioned reviews have identified improvements in disease activity, anxiety, depression, quality of life, and coping when cognitive-behavioural therapy (CBT) was provided to patients with clinically significant anxiety and depression. For example ; Jordan et al, 2018, investigated the clinical benefits of a non-randomised uncontrolled trial of clinic based cognitive behaviour therapy (CBT) for adults with IBD who had moderate to severe levels of anxiety and low mood and compared the results to a previous randomised controlled trial of CBT in this population. Previous randomised controlled trials had found no evidence that psychological interventions enhanced outcomes for people with IBD but had recruited patients without distress (Timmer et al, 2011). The results of this study identified statistically significant improvements to mood, quality of life and	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. Quality of life was included in the protocol for this guideline update as an outcome but there was limited evidence on this outcome. Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed your comment on to the

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				symptomatic disease activity and uncontrolled effect sizes were superior to those of the RCT. This suggested that CBT may have benefits for those with moderate to severe disturbances to mood and that the effect sizes of RCT's could be improved by targeting those with distress. Mikocka-Walus et al 2012, investigated the impact of implementing a biopsychosocial model of care for IBD in a hospital-based cohort of patients. This included the provision of CBT for patients with UC & CD identified as experiencing moderate to severe anxiety and depression. This study found that patients with documented psychological comorbidities were more likely to be hospitalized than those without (odds ratio [OR] ¼ 4.13, 95% confidence interval [CI]: 1.25, 13.61). Improvements in disease activity, anxiety, depression, quality of life, and coping were found when cognitive-behavioural therapy (CBT) was provided to patients. A drop in the use of opiates (P ¼ 0.037) and hospitalization rates (from 48% to 30%) in IBD patients were noted as a result of introduction of the changed model of care. In addition, the mean total cost of inpatient care was lower for IBD patients than controls (US$12,857.48 [US$15,236.79] vs. US$ 30,467.78 [US$ 53,760.20], P ¼ 0.005).	surveillance team for consideration in future updates.
British Association for Behavioural and Cognitive Psychotherapies (BABCP)	Guideline	12	16 continued	Given the established association between anxiety, low mood and disease activity and the potential impact that CBT may have on improving these outcomes, it is advisable to recommend the consideration of the role of mood on the course of UC and CD in the guidelines for inducing remission in UC and CD. Symptoms of anxiety, depression and quality of life could potentially be assessed through self-report measures and monitored throughout treatment. This may be of particular importance for people who are experiencing prolonged periods of disease activity. Referrals to psychological services for potential treatment could be facilitated for those people found to be experiencing persistent disturbance to mood. Early identification and management of psychological distress could prevent disturbances in mood and quality of life from negatively influencing outcomes for people with IBD.	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. Quality of life was included in the protocol for this guideline update as an outcome but there was limited evidence on this outcome. Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed your comment on to the surveillance team for consideration in future updates.
British Association for Behavioural and Cognitive Psychotherapies (BABCP)	Evidence review	All		Additional references: Filipović B R., Filipović B F., Kerkez M., Milinić N., Randelović T. (2007).Depression and anxiety levels in therapy-naive patients with inflammatory bowel disease and cancer of the colon. World J Gastroenterology. 13(3), pp 438-43. Graff, L. A., Walker, J., Lix, R., Clara, L., Rawsthorne, I., Rogala, P., Miller, L., Jakul, N., McPhail, L., Ediger, C., Bernstein, J. (2006). The Relationship of Inflammatory Bowel Disease Type and Activity to Psychological Functioning and Quality of Life. Clinical Gastroenterology and Hepatology 4 (12), pp1491-1501. Jordan, C., Sin, J., Fear, N.T. & Chalder, T. (2016) A systematic review of the psychological	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed these references to the surveillance team for consideration in future updates.

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				correlates of adjustment outcomes in adults with inflammatory bowel disease. Clinical Psychology Review. Jordan C., Ohlsen R., Hayee B., Chalder T. (2017). A qualitative study exploring the experience of people with IBD and elevated symptoms of anxiety and low mood and the type of psychological help they would like, Psychology & Health, pp 1-18. Cheryl Jordan, Bu 'Hussain Hayee & Trudie Chalder, (2018). Cognitive behaviour therapy for distress in people with Inflammatory Bowel Disease: A bench marking study. Clinical psychology and psychotherapy. Kemp K., Griffiths J., Lovell, K. (2012). Understanding the health and social care needs of people living with IBD: a meta-synthesis of the evidence. World J gastroenterol. 18(43), pp6240-6249. Knowles, S., Monshat, K., Castle, D., 2013. The Efficacy and Methodological Challenges of Psychotherapy for Adults with Inflammatory Bowel Disease: A Review. Inflammatory Bowel Diseases, 19(12) pp2704-2715. Mikocka-Walus A, Pittet V., Rossel JB., Von Känel R; Swiss IBD Cohort Study Group. (2016). Symptoms of Depression and Anxiety Are Independently Associated With Clinical Recurrence of Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2016 Jun;14(6):829-835.e1 Mikocka-Walus AA[1], Turnbull D, Holtmann G, Andrews JM. An integrated model of care for inflammatory bowel disease sufferers in Australia: development and the effects of its implementation. Inflamm Bowel Dis. 2012 Aug;18(8):1573-81. doi: 10.1002/ibd.22850. Epub 2011 Dec 16. Mittermaier, C., Dejaco, C., Waldhoer, T., Oefferlauber-Ernst, A., Miehsler, W., Beier, M., Tillinger, W., Gangl, A., Moser, G. (2004). Impact of depressive mood on relapse in patients with inflammatory bowel disease: A prospective 18-month follow-up study. Psychosomatic Medicine 66(1), pp 79-84. Timmer, A., Preiss, J. C., Motschall, E., Rücker G., Jantschek G., Moser G. (2011). Psychological interventions for treatment of inflammatory bowel disease (Review). The Cochrane Library (8). Walker JR., Ediger JP., Graff LA., Greenfeld JM., Clara I., Lix L., Rawsthorne P., Miller N., Rogala L., McPhail CM., Bernstein CN., (2008). The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. Am J Gastroenterol. Aug; 103(8)	
British Association for Behavioural and Cognitive Psychotherapies (BABCP)				Timmer, A., Preiss, J. C., Motschall, E., Rücker G., Jantschek G., Moser G. (2011). Psychological interventions for treatment of inflammatory bowel disease (Review). The Cochrane Library (8).	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed these references to the

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					surveillance team for consideration in future updates.
British Association for Behavioural and Cognitive Psychotherapies (BABCP)				Walker JR., Ediger JP., Graff LA., Greenfeld JM., Clara I., Lix L., Rawsthorne P., Miller N., Rogala L., McPhail CM., Bernstein CN., (2008). The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. Am J Gastroenterol. Aug; 103(8)	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. Psychological interventions were not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed these references to the surveillance team for consideration in future updates.
British Dietetic Association (BDA)	Research recommendations	16	2-6	We fully agree that there should be more research on the use of enteral nutrition to maintain disease remission in Crohn's disease. However, there are quite a few groups now looking at inducing disease remission with whole food diets rather than enteral nutrition alone. Whole food diets are much better tolerated and highly acceptable for patients with Crohn's disease. This is an exciting new area of research and it may be better to broaden the research recommendation to include all types of diets to maintain disease remission post-surgery. For example, the research recommendation could read: 1 Diet after surgery What are the benefits, risk and cost effectiveness of using diet (e.g. enteral nutrition, whole foods) in maintaining remission in the post-surgical period of Crohn's disease? The references related to novel diet treatments are: Svolos V et al Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. Gastroenterology. 2018 Dec 11. pii: S0016-5085(18)35398-8. doi: 10.1053/j.gastro.2018.12.002. [Epub ahead of print] Sigall Boneh R et al Dietary Therapy With the Crohn's Disease Exclusion Diet is a Successful Strategy for Induction of Remission in Children and Adults Failing Biological Therapy. J Crohns Colitis. 2017 Oct 1;11(10):1205-1212. doi: 10.1093/ecco-jcc/jjx071. Sigall Boneh R et al Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. Inflamm Bowel Dis. 2014 Aug;20(8):1353-60. doi: 10.1097/MIB.0000000000000110.	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. Whole food diets and other types of diets were not considered as part of this guideline update; we have not searched for existing evidence for other types of diets and therefore we are unable to make this addition to the research recommendation. We have passed your comment on to the surveillance team for consideration in future updates.

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British Dietetic Association (BDA)	Rationale and impact	17	13-15	The rationale and impact section for the above could read: There was no randomised controlled trial evidence on any kind of dietary intervention including whole food diets and enteral nutrition. The committee recommended further research on this because diet is sometimes used alone or with other maintenance therapy for maintaining remission after surgery. Patients often seek non-evidenced based information on diet which is available online and will over-restrict their diet leading to further nutritional limitations (e.g. nutrient deficiency)	Thank you for your comment. Whole food diets were not considered as part of this guideline update and therefore we are unable to make this addition to the research recommendation.
British Society for Antimicrobial Chemotherapy		General	General	No comments	Thank you.
British Society of Gastroenterology	Guideline	General	General	We have serious concerns that this guideline update, as drafted, does not reflect current practice or the comprehensive and evidence-based British Society of Gastroenterologists (BSG) Inflammatory Bowel Disease (IBD) guidelines and consensus-based IBD Standards, which have been collaboratively developed by 17 professional and patient organisations, both of which are very soon to be published and have been developed in alignment with each other. We strongly believe that the next stage of the guideline update should be delayed enabling full consideration of and alignment with the BSG IBD guidelines and IBD Standards. Without this, the delivery of high-quality treatment and care for people with Crohn's Disease and Ulcerative Colitis could be impeded. Alternatively, NICE guidelines that support and align with the BSG guidelines and IBD Standards will significantly enhance this.	NICE is aware of the forthcoming BSG IBD guideline. NICE and the BSG have met to discuss the synergies and overlaps in the 2 organisations' portfolios for gastroenterology topics. For this particular guideline the update covers only the maintenance of remission following surgery in Crohn's disease. Following the publication of the BSG guideline NICE will consider the impact on the Crohn's disease guideline.
British Society of Gastroenterology	Guideline	6	9	We are concerned that there is a lack of good evidence to support the recommendation of a 5-ASA for exacerbations of Crohn's for patients who can't have steroids.	Thank you for your comment. Induction of remission was out of the scope of this updateand therefore we are unable to address comments on this part of the guideline.
British Society of Gastroenterology	Guideline	6	9	We are also concerned that the 5-ASA is not mentioned as a maintenance agent, only as an induction agent.	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. We are unable to address comments on other parts of the guideline that fall outside the scope of the update.

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British Society of Gastroenterology	Guideline			For Crohn's I have the following points:	Thank you.
British Society of Gastroenterology	Guideline	6	1	The preference of prednisolone over Budesonide for mild to moderate ileal disease is very old fashioned given side effect profiles.	Thank you for your comment. Induction of remission was out of the scope of this guideline update and therefore we are unable to address comments on this part of the guideline.
British Society of Gastroenterology	Guideline	General	General	5-ASA should never be offered for CD. The evidence for any effect is very poor and does not in our opinion represent a good cost effective treatment	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. In the post-surgical setting, the committee did not recommend 5-ASA (mesalazine) to maintain remission as there was insufficient evidence of its clinical and cost effectiveness. Induction of remission was out of the scope of this guideline update and therefore we are unable to address comments about the recommendation for 5-ASA in this part of the guideline. We will pass your comment to the surveillance team for consideration duringthe next update.
British Society of Gastroenterology	Guideline	General	General	It is our opinion that the introduction of azathioprine comes too late in the algorithm. Most gastroenterologists would recommend a steroid sparing agent when more than a single course of steroids is needed in a single calendar year. All the members of the IBD section committee of the British Society of Gastroenterology have agreed this definition.	Thank you for your comment. This guideline update only considered evidence on pharmacological treatments for post-surgical maintenance of remission and enteral nutrition for post-surgical maintenance of remission. Induction of remission was out of the scope of this update and therefore we are unable to make changes to this part of the guideline.

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British Society of Gastroenterology	Guideline	General	General	Why are infliximab and adalimumab guidance described in detail and Ustekinumab and vedolizumab just links?	Thank you for your comment. The technology appraisal TA187 for infliximab and adalimumab has been moved to the 'static list' and will not be updated in the future as a technology appraisal. This means the recommendations from the TA can be either incorporated or updated as part ofa relevant NICE guideline. TA456 (ustekinemab) and TA352 (vedolizumab) have not been moved to the static list and therefore they could be subject to future updates by the Technology Appraisals programme. In these cases, a link has been inserted to cross-refer to the TA so that if the TA is updated and the recommendations change, the guideline will refer readers to the most up to date recommendations.
British Society of Gastroenterology	Guideline	General	General	Post surgery is very restrictive for some patients with on-going microscopic disease etc. or high risk profile anti-TNF should be given.	Thank you for your comment. The recommendations reflect the evidence that was available as the populations in the clinical trials were mainly people who had undergone complete macroscopic resection. Biologics were not cost effective for maintaining remission in these people.. We have expanded the rationale and impact section of the guideline to make clear that these recommendations only apply to people whose disease is in remission after surgery. Section 1.2 of ot he guideline provides recommendations for inducing remission in people with active disease.
British Society of Gastroenterology	Guideline	15	12	Would consider that the Pregnancy section is again pointless. It is too short and in not enough detail to be of value	Thank you for your comment. Conception and pregnancy was not considered as part of this guideline update and therefore we are unable to make changes to this area.
British	Guideline	Gener	Gene	Other comments from out committee included comments such as - These draft guidelines seem a	Thank you for your comment. This

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Society of Gastroenterology		al	ral	bit antiquated e.g. recommendation for 5-ASAs in CD is astonishing	guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. In the post-surgical setting, the committee did not recommend 5-ASA (mesalazine) to maintain remission as there was insufficient evidence of its clinical and cost effectiveness. Induction of remission was out of the scope of this guideline update and therefore we are unable to address comments about the recommendation for 5-ASA in this part of the guideline.
British Society of Gastrointestinal & Abdominal Radiology	1.2.16			Specifically add imaging as an option	Thank you for your comment. Induction of remission was not considered as part of this guideline update and therefore we are unable to make changes to this area.
British Society of Paediatric gastroenterology Hepatology and nutrition (BSPGHAN)]	Guidelines	12	General	Recommendation 1.4.1 Azathioprine and metronidazole after Crohn's surgery The guidelines make a main recommendation to consider Azathioprine with metronidazole. This is the first recommendation and we cannot see any strong supporting evidence for it. In the D'Haens paper, we find the risk of bias assessment troubling, with allocation concealment noted as low risk, and however we find no support for this in the paper with only inference. We also agree that the blinding is problematic. We note therefore the low / very low GRADE ranking. Given the recommendation is based on the single study and therefore the major issues with imprecision with a total patient number of 80 and 25% of patients and only a 1 year follow up, we cannot see the rationale for this recommendation. The clinical relapse data does not provide strong support for this recommendation. In their 1 year study, according to ITT, the study did not find a statistically significant favouring this combination. The NICE evidence team have found the same on page 164-166 of the evidence report, with this not significant in the NMA analysis and so how can such a treatment, tested in one small trial, with very low GRADE ranking, risk of bias concerns in the most serious areas, high attrition for a short trial, with follow up of just 12 months and no significant result favouring the impact on clinical relapse be the main proposal. There are safety concerns associated with Azathioprine as well. Whilst such a small study size prevents conclusions due to	Thank you for your comments. Risk of bias was assessed using the Cochrane risk of bias checklist. D'Haens 2008 states: "randomization took place in the pharmacy of the Leuven University Hospitals within 2 weeks after surgery. The random allocation sequence was delivered by a randomization program written in Visual Basic version 6". From this, allocation concealment was graded as low risk of bias. The current review identified 3 studies that assessed the use of azathioprine in combination with 3 months of metronidazole: D'Haens (2008), Manosa (2013) and Lopez-Sanroman (2017). The network meta-analysis showed a significant benefit for azathioprine + metronidazole

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				imprecision of such rare events, the trend is all against Azathioprine. Our suggestion is to move this to the further research section and is not a recommendation.	compared to placebo for the outcome endoscopic relapse. The committee prioritised endoscopic relapse as the most important outcome because it is an objective measure of disease and because the goal of treatment in Crohn's disease has shifted from symptom relief alone towards mucosal healing. For both endoscopic and clinical relapse, all the treatments that ranked ahead of azathioprine + metronidazole in the network meta-analyses included a biologic agent. The economic model showed that regimens containing biologics were not cost effective and the committee agreed they could not be recommended for post-surgical maintenance of remission. Therefore, the combination of azathioprine + metronidazole was the most clinically effective treatment after biologics that was also shown to be cost effective. 12 months was the most common duration of follow-up reported across trials for the outcome endoscopic relapse. A number of trials, particularly for the biologic agents, had smaller sample sizes than D'Haens (2008). Overall uncertainty in the estimates of relative effects in the network meta-analyses led the committee to make a 'consider' recommendation as opposed to a stronger 'offer' recommendation for azathioprine and metronidazole.
British Society of Paediatric gastroenterology Hepatology and	Guidelines	13	General	Recommendation 1.4.2 Consider Azathoprine after Crohn's surgery if metronidazole not tolerated. We note the NMA results on page 164-168 and these show no results in favour of Azathioprine for either clinical or endoscopic remission / relapse. It is also worth noting that despite the risk of bias concerns with Dheans, as stated above, the remaining studies are of good ranking and on meta-analysis, imprecision concerns were dealt with,	Thank you for your comment. The protocol defined withdrawal due to adverse events as an outcome of interest for the review. The committee did not specify individual adverse events and did not specifically search for data on pancreatitis. There was considerable uncertainty in the results of

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nutrition (BSPGHAN)]				so we believe the certainty / consistency of this negative result is probable. The individual meta-analysis on pages 130-133 finds similar lack of evidence. As such, we would propose no such recommendation for Azathioprine and particularly would propose closer safety scrutiny with close to significant increased events of withdrawal in all studies and particular attention needed for pancreatitis, particularly in children, given the relative risk seems a 20-50 increase in all thiopurine studies. There is no mention of 6MP. The recent study by Mowat et al in the UK (Mowat C, Arnott I, Cahill A et al *Lancet Gastroenterol Hepatol 2016; 1:273-82*) which is showed as a significant result in the network, we are surprised this is missing from the recommendations and indeed there seems to be stronger evidence for 6MP than the none existent evidence for AZA. We would propose this is added as a recommendation.	the network meta-analysis for withdrawal due to adverse events, as suggested by the wide credible intervals for many of the treatments. The committee recommended azathioprine plus metronidazole as first-line treatment. It was aware that some patients may not be able to tolerate metronidazole. Although azathioprine did not show a statistically significant benefit compared to placebo in the NMAs for clinical and endoscopic relapse, the point estimates for the hazard ratios for both outcomes favoured azathioprine. Taking into account uncertainty around the treatment effects for all comparators in the cost-effectiveness scenario analysis without metronidazole, azathioprine generated more health benefits in terms of total QALYs and lower total costs compared to no treatment, budesonide and mesalazine and had a 72% proability of being cost effective at a threshold of £20,000/QALY. This same scenario analysis showed that although mercaptopurine was more effective than azathioprine at reducing endoscopic relapse, it is not cost effective at its current price. Therefore the committee recommended azathioprine alone for people who cannot tolerate metronidazole. Due to concerns raised by stakeholders about potential adverse effects of both azathioprine and metronidazole, the committee agreed to add a new recommendation to reinforce the need to monitor the effects of azathioprine and metronidazole, including monitoring neutropenia levels in those taking

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					azathioprine, and the need to have safety protocols in place. We note your concerns regarding children. None of the included studies addressed this population, however the committee agreed that it was appropriate to extrapolate the evidence to children because in practice children and adults are treated the same way.
British Society of Paediatric gastroenterology Hepatology and nutrition (BSPGHAN)]	Guidelines	13	General	Recommendation 1.4.4 biologics after surgery We note the guidelines are not recommending the use of these agents based on the evidence and the economic analysis. However it is worth adding that many patients with Crohn's disease who had complete macroscopic resection of their luminal disease could have extra-luminal manifestations (perianal Crohn's disease) and extra-intestinal manifestations (arthritis, skin manifestations) kept under control on biologics treatment. These patients will benefit from continuation of the biologics treatment. Could this point be clarified in the guidelines please? Given particularly the results in the Network meta-analysis on page 166 for clinical remission, page 174 for endoscopic remission and in particular the extremely positive risk ratios involved, we believe a recommendation for further research is needed.	Thank you for your comment. The rationale and impact section of the guideline has been updated to make it clear that these recommendations are for maintaining remission after surgery. People who have active disease after surgery are not in remission and should be treated according to the recommendations in Section 1.2 of the guideline on inducing remission.
British Society of Paediatric gastroenterology Hepatology and nutrition (BSPGHAN)]	Table 1	20	Row 2	It is noted in table 1, the guidelines deleted ' consider 5-ASA after surgery' as 'This recommendation has been deleted because the committee agreed the newer evidence favoured azathioprine'. We have concerns about this decision. The 'new' evidence should never be a core reason to support such recommendations. Instead, the merit of the evidence from any time, including risk of bias, GRADE ranking, etc should guide such decisions. We note in the meta-analysis on page 122 there is no relapse or remission data for Brignola 1997 study or the Mcleod 1995, however this is clearly available in the paper and indeed were deemed homogenous enough to analyse for adverse events on page 124. On page 106 why Mcleod is missing from the clinical evidence table? Clearly, it has had Risk of bias judgements and safety data used in analysis, so we presume this is a	Thank you for your comments. Table 1 is a brief summary of the changes produced to the guideline as a result of this update. All relevant evidence that met the inclusion criteria for the review question, not only newer data, was considered in developing the recommendations, along with the expertise of the guideline committee. The evidence from the network meta-analyses did not show a clear benefit for mesalazine and the economic analysis showed mesalazine is unlikely to be cost effective. For these reasons, the 2012 recommendation was removed and the

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				mistake.	committee agreed not to recommend aminosalicylates, including mesalazine. The Brignola 1995 study (there was no Brignola 1997 study in the evidence review) is included in the pairwise results for clinical remission (p.122), endoscopic remission and withdrawal due to adverse events. The McLeod 1995 study does not appear in the pairwise results for clinical remission because only clinical relapse was reported in the study and it was not possible to confidently derive the number of patients in remission. This was explained on p.160 of the evidence report. Thank you for pointing out that McLeod 1995 was missing from the clinical evidence table (Appendix F). This has been corrected in the report.
CICRA (Crohns in Childhood Research Association)	Guideline	5	24-27	The statements on enteral nutrition are too weak. This is the standard induction treatment in paediatric Crohn's disease in the UK and across Europe. It's also recommended in the ESPGHAN/ECCO guidance: https://www.ecco-ibd.eu/images/6_Publication/6_3_ECCO%20Guidelines/MASTER_JCC_ECCO-ESPGHAN_Consensus_PaediatricCD_Issue10_Vol8.pdf). The continued qualifiers about growth are therefore not required or appropriate.	Thank you for your comment. Induction of remission was not considered as part of this guideline update and therefore we are unable to make changes to this area.
CICRA (Crohns in Childhood Research Association)	Guideline	6	9-16	This continued inclusion to support non-evidence based practice is disappointing. (See Cochrane review on induction: https://www.ncbi.nlm.nih.gov/pubmed/27681657 and systematic review against budesonide for induction and remission: https://www.ncbi.nlm.nih.gov/pubmed/25864873 amongst others).	Thank you for your comment. Induction of remission was not considered as part of this guideline update and therefore we are unable to make changes to this area. We have passed your comment on to the surveillance team for consideration in future updates.
Crohn's & Colitis UK	General	General	General	We have serious concerns that this guideline update, as drafted, does not reflect current practice or the comprehensive and evidence-based British Society of Gastroenterology (BSG) Inflammatory Bowel Disease (IBD) guidelines and consensus-based IBD Standards, which have been collaboratively developed by 17 professional and patient organisations, both of which are very soon to be published and have been developed in alignment with each other.	**NICE is aware of the forthcoming BSG IBD guideline. NICE and the BSG have met to discuss the synergies and overlaps in the 2 organisations' portfolios for gastroenterology topics.**

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				We strongly believe that the next stage of the guideline update should be delayed enabling full consideration of and alignment with the BSG IBD guidelines and IBD Standards. Without this, the delivery of high-quality treatment and care for people with Crohn's Disease and Ulcerative Colitis could be impeded. Alternatively, NICE guidelines that support and align with the BSG guidelines and IBD Standards will significantly enhance this. *The position above is shared by Crohn's & Colitis UK and the British Society of Gastroenterology* BSG BRITISH SOCIETY OF GASTROENTEROLOGY CLINICAL SERVICES CROHN'S & COLITIS UK FIGHTING INFLAMMATORY BOWEL DISEASE TOGETHER In Spring 2019 IBD UK will be launching a refreshed version of the IBD Standards. The IBD Standards are collaboratively developed between 17 professional and patient organisations, following the Delphi consensus method, in alignment with BSG guidelines. The Standards cover the IBD Service, Pre-Diagnosis, Flare Management, Surgery, Inpatient Care and Ongoing Care. A newly launched national patient survey and benchmarking tool will enable IBD services to benchmark their care against the IBD Standards, informed by the experience of patients using their service. The BSG will also be launching a new version of the BSG IBD guidelines. The BSG IBD guidelines are based on an extensive literature review, widespread involvement across all relevant professional disciplines, including patient and patient organisation involvement and input and a robust consensus process. Crohn's & Colitis UK also want to share some concerns that have arisen regarding the consultation process itself. The deadline given to respond to two significant consultations over the Christmas period has inhibited our organisation's ability to respond effectively, and to engage with members and stakeholders. We are concerned that this element of the guideline review has not been given sufficient time, with limited meaningful proactive stakeholder engagement. We also wish to note that we have been disappointed by the Committee secretariat's lack of communication and response to enquiries.	**For this particular guideline the update covers only the maintenance of remission following surgery in Crohn's disease. Following the publication of the BSG guideline NICE will consider the impact on the Crohn's disease guideline.** This guideline update only reviewed evidence on pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. This area was prioritised for update because new evidence was identified that could have an impact on recommendations. Your feedback on the timeline for the consultation process have been passed to the relevant team in NICE for consideration.
Crohn's & Colitis UK	Guideline	General	General	There are a number of areas - aligned with pathways and the patient journey - that are unclear (as currently drafted): - identification and referral pathway (see also comment below)	Thank you for your comment. This part of the guideline was out of the scope of the update and therefore we are unable to

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				- preventing and managing a flare or relapse (picking up on the link between primary and secondary care) - role of the IBD nurse and multidisciplinary team - personalised care planning We recommend revisiting this guideline to bring it in line with the IBD Standards and ensure that newly diagnosed outpatients start treatment rapidly, given the established and accepted implications of delayed treatment (poorer prognosis, increased likelihood of surgery and use of more expensive drug treatments). We would recommend, based on current good practice, that a treatment plan should be started within 48 hours for moderate to severe symptoms and within two weeks for mild symptoms..	make changes to it.
Crohn's & Colitis UK	Guideline	1	6	We strongly recommend that this guideline signposts healthcare professionals and commissioners to NICE guidance on the use of faecal calprotectin to support the identification and appropriate referral of Inflammatory Bowel Disease and ensure early and accurate diagnosis. https://www.nice.org.uk/guidance/dg11	Thank you for your comment. Identification and referral was outside of the scope of this update and therefore we are unable to make changes to it.
Crohn's & Colitis UK	Guideline	1	6	We would strongly suggest adding a reference to the NICE quality standard for inflammatory bowel disease QS81 both in the introduction and throughout the document. We would also suggest specifying how the updated guideline and quality standard correlate to each other in terms that members of general public will understand.	Thank you for your comment. There will be a link to the NICE quality standard from the main webpage of this guideline.
Crohn's & Colitis UK	Guideline	1	6	We are concerned that the guideline as currently drafted does not include 'self-management' as part of its main specified aims. Given the Government's emphasis on the importance of self-management (NHS Long-Term Plan, 2020 Vision (NHS Scotland) and Healthier Wales)) and the important role that supported self-management plays in patient experience, prevention and better clinical outcomes, we believe it should be a clear aim of the guideline and subsequent guidance. Crohn's & Colitis UK's position on self-management can be supplied on request.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. We have passed your comment on to the surveillance team for consideration in future updates.
Crohn's & Colitis UK	Guideline	4	1	We suggest that this section should be revised in line with the IBD Standards and the principles of shared decision making. Patients should be supported to make informed, shared decisions about their treatment and care to ensure these take their ***preferences and goals*** fully into account. Patients should be given timely, clear information and the right support to be enabled to decide the acceptability of treatment options and potential complications, have realistic expectations and understand possible (and optimal) outcomes. As such, shared decision making is very important and we would suggest that it is reproduced	Thank you for your comment. Patient information and support was not considered as part of this guideline update and therefore we are unable to make changes to this area. NICE is about to begin development of a guideline on shared decision making and we would encourage you to register as a

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				clearly in this document, rather than signposted to on other pages of the NICE website. The guideline as currently written assumes greater understanding of shared decision making than should be expected of the general public, especially children and young people.	stakeholder for this guideline on the NICE website.
Crohn's & Colitis UK	Guideline	4	3	In line with the IBD Standards, we suggest adding that *patients should be provided with information in a format and language they can easily understand which is made available at every point of their journey*. Regarding the latter point, the guidelines should seek to reflect that information provided at the time of diagnosis may be different to further along in their journey. Information will need to be revisited, explained and reissued with changes to treatment, understanding and practice. In line with the IBD Standards, **rapid access to specialist advice** should be available to patients who are experiencing a flare, including access to a telephone/email advice line with an end of the next working day turnaround. The 'Providing information and support' section should also ***extend to providing information and support about the IBD service itself***, and not limited to just the condition. The IBD Standards state: *All IBD patients should have information describing the IBD service and how it can be accessed. This should include information on how patients who have concerns about their condition or their care can request discussion of their case at the IBD team meeting or request a second opinion. It should also explain how patients can give feedback on the care they receive or participate actively in service development/quality improvement (in line with government policies).* Furthermore, all patients should be provided with a point of contact, and clear information about pathways and timescales while awaiting the outcome of tests and investigations.	Thank you for your comment. Patient information and support was not considered as part of this guideline update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	4	4	In line with the BSPGHAN guidelines on Inflammatory Bowel Disease, we suggest the guidelines are amended to reflect that any specialty service must be arranged around the needs of the child and family with the child receiving the highest quality care but as close to home as possible (e.g. outreach clinics) as part of a managed clinical network. https://bspghan.org.uk/guidelines https://bspghan.org.uk/sites/default/files/guidelines/IBDGuidelines.pdf	Thank you for your comment. Patient information and support was not considered as part of this guideline update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	4	7	Add a reference to the NICE quality standard on inflammatory bowel disease, QS81.	Thank you for your comment. The NICE Quality standard QS81 will be linked to

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				In line with the IBD Standards, patients should be fully informed about the benefits and risks of, and the alternatives to, immunomodulator and biological therapies, including surgery.	from the main webpage of this guideline.
Crohn's & Colitis UK	Guideline	4	9	Add a reference to the NICE quality standard on inflammatory bowel disease, which specifies that *services provide age-appropriate support from a multidisciplinary team for people with inflammatory bowel disease, and their family members or carers.*	Thank you for your comment. The NICE Quality standard QS81 will be linked to from the main webpage of this guideline.
Crohn's & Colitis UK	Guideline	4	10	Add a reference to (NICE) guidance on shared decision making.	Thank you for your comment. Providing information and support was not considered as part of this guideline update and therefore we are unable to make changes to this area. NICE is about to begin development of a guideline on shared decision making and we would encourage you to register as a stakeholder for this guideline on the NICE website.
Crohn's & Colitis UK	Guideline	4	10	In line with the IBD Standards, clinicians should advise patients about relevant shared care arrangements.	Thank you for your comment. Providing information and support was not considered as part of this guideline update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	4	14	We are concerned that this list has not been reviewed to take into consideration any new and relevant guidelines that have been published by NICE since 2012. In line with the IBD Standards, we would suggest that this section should also signpost to the following NICE publications: 1) mental health and well-being (2) Diet, nutrition and obesity (3) Physical activity (4) Corticosteroids (5) Workplace health/long-term sickness	Thank you for your comment. Providing information and support was not considered as part of this guideline update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	5	2	In line with the IBD Standards, all patients with IBD should be provided with clear information to support: • self-management • early intervention in the case of a flare. • signposting to education, groups and support • social prescribing Additionally, clear information about IBD, the local IBD Service and patient organisations should be accessible in outpatient clinics, wards, endoscopy and day care areas.	Thank you for your comment. Providing information and support was out of the scope of this update and therefore we are unable to make changes to this area.

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				Patients or parents/carers should be offered copies of clinical correspondence relating to their/their child's treatment and care. In line with NHS England guidance, all patients should have a written personalised care plan.	
Crohn's & Colitis UK	Guideline	5	10	In line with the IBD Standards, patients being considered for surgery should be offered written, audio-visual or web-based information. Where possible, they should have the opportunity to talk with patients who have had surgery. They should also be provided with information about their post-operative care before discharge and offered psychological support.	Thank you for your comment. Providing information and support was out of the scope of this update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	5	11	In line with the IBD Standards, patients should have a transition coordinator who is responsible for the preparation and oversight of transition (for example, an IBD Nurse Specialist) and protocols should be in place which clearly define the local transition service and the personnel responsible. Crohn's & Colitis UK has produced information for young people and parents to support transition into adult services.	Thank you for your comment. Providing information and support was out of the scope of this update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	5	13	In line with the IBD Standards, insert mental health and wellbeing.	Thank you for your comment. Providing information and support was out of the scope of this update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	general	general	We would question the evidence base for the use of 5-ASAs in Crohn's. Cochrane review - https://www.cochrane.org/CD003715/IBD_oral-5-aminosalicylic-acid-drugs-maintenance-medically-induced-remission-crohns-disease	Thank you for your comment. This guideline update only considered pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. In the post-surgical setting, the committee did not recommend 5-ASA (mesalazine) to maintain remission as there was insufficient evidence of its clinical and cost effectiveness. Induction of remission and maintenance of medically-induced remission were out of the scope of this update and therefore we are unable to address comments about the recommendation for 5-ASA in these parts of the guideline.
Crohn's & Colitis UK	Guideline	8	4	Clear protocols should be in place for the supply, monitoring and review of medication across primary and secondary care settings.	Thank you for your comment. This guideline update only considered evidence

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					on treatments for post-surgical maintenance of remission. As part of the current update, we are unable to make changes to other recommendations where the evidence has not been reviewed.
Crohn's & Colitis UK	Guideline	10	21	There is a clear and significant imbalance in the information that is provided on biologics. While there is a detailed section on the use of infliximab and adalimumab, scant information is provided on alternative biological drug treatements. As such, this section as currently written would not support patients to make an informed decision about their treatment. We would recommend revising this section to support clearer decision making and understanding of the range of treatment options. In line with the IBD Standards and BSG IBD guidelines, we would also recommend directing healthcare professionals and commissioners to have protocols in place protocols for pre-treatment tests, vaccinations, prescribing, administration and monitoring of biological therapies. We would also ask that the committee consider directing healthcare professionals and commissioners to record and audit the use of biologics through the IBD Registry, which is currently part of the Quality Accounts and would bring this section into line with the IBD Standards.	Thank you for your comment. The technology appraisal TA187 for infliximab and adalimumab has been moved to the 'static list' and will not be updated in the future as a technology appraisal. This means the recommendations from the TA can be either incorporated or updated as part ofa relevant NICE guideline. TA456 (ustekinemab) and TA352 (vedolizumab) have not been moved to the static list and therefore they could be subject to future updates by the Technology Appraisals programme. In these cases, a link has been inserted to cross-refer to the TA so that if the TA is updated and the recommendations change, the guideline will refer readers to the most up to date recommendations. This guideline update only considered evidence on treatments for post-surgical maintenance of remission. As part of the current update, we are unable to make changes to other recommendations where the evidence has not been reviewed
Crohn's & Colitis UK	Guideline	10	29	Patients should be fully informed about the benefits and risks of, and the alternatives to, immunomodulator and biological therapies, including surgery. Notes of the person's view should also be included in their personal care plan (as appropriate).	Thank you for your comment. Maintenance of medically-induced remission was not considered as part of this guideline update and therefore we are unable to make changes to this area.
Crohn's & Colitis UK	Guideline	11	5	In order to be consistent with the Ulcerative Colitis guideline, information about the risk of developing colorectal cancer and about colonoscopic surveillance to the person, their family	Thank you for your comment. This part of the guideline was out of the scope of this

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				members or carers should be added, as should a reference to the NICE guideline on suspected cancer: recognition and referral. Additionally, in line with the IBD Standards, all IBD patients should be reviewed at agreed intervals by an appropriate healthcare professional and relevant disease information recorded.	update and therefore we are unable to make changes to it.
Crohn's & Colitis UK	Guideline	11	22	See previous comments on shared care. We would recommend adding a reference to shared care to this section.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Crohn's & Colitis UK	Guideline	12	16	This section should reference the NICE quality standard on inflammatory bowel disease QS81, which states: *People having surgery for inflammatory bowel disease have it undertaken by a colorectal surgeon who is a core member of the inflammatory bowel disease multidisciplinary team.*	Thank you for your comment. The NICE Quality standard QS81 will be linked to from the main webpage of this guideline. Surgery was not considered as part of this guideline update and therefore we are unable to make changes to recommendations about who should undertake surgery.
Crohn's & Colitis UK	Guideline	13	3-8	We would question the evidence supporting this recommendation and its wording. We believe that it is over restrictive and not in the best interests of patients. It is unclear whether the recommendation is referring to patients who were prescribed biologics before their surgery or patients who were not prescribed biologics before their surgery, or both. Furthermore, it is unclear what this recommendation would mean for patients who are receiving biologics to treat extra-intestinal manifestations (or complications) of their disease or those with metastatic Crohn's disease. Overall, there will be circumstances in which a patient should continue to receive biologics and these should be clearly stated.	Thank you for your comment. The evidence showed that biologics are not cost effective for maintaining remission in people with ileocolonic Crohn's disease who have had complete macroscopic resection. This recommendation is irrespective of whether or not a person was receiving biologics before surgery. This recommendation does not apply to people who may be receiving a biologic for reasons other than to maintain remission after ileocolonic resection.For people who have active disease after surgery, Section 1.2 of the guideline provides recommendations for inducing remission.
Crohn's & Colitis UK	Guideline	13	12	In line with the IBD Standards and national treatment targets, elective surgery for IBD should be performed as soon as the patient's clinical status has been optimised and within 18 weeks of referral for surgery. Patients and parents/carers should be provided with information about post-operative care before discharge, including wound and stoma care, and offered psychological and rehabilitation support.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.

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Crohn's & Colitis UK	Guideline	13	13	The information provided in this section is limited and does not align with the depth of information and support advocated in the guidelines for the treatment of Ulcerative Colitis. We would recommend that this section is revisited. The omission of detailed and relevant information/aftercare is striking and concerning. This recommendation does not reflect current practice, training and good practice and should be bought in line with the NICE quality standard on inflammatory bowel disease, BSG IBD guidelines and IBD Standards. Recommendations should include: • Elective IBD surgery should be performed by a recognised colorectal surgeon • The surgeon should be a member of the IBD team • The unit should undertake these kinds of operations regularly. In the absence of relevant local expertise, complex surgery should be referred to a specialist unit. • Patients should have access to age appropriate expertise and advice • There should be regular combined or parallel clinics bringing together medical and surgical teams There should be opportunities to: • Receive specialist counselling • Access specialist opinion regarding reconstructive surgery • To meet with people (and families) of a similar age who have experienced surgery (particularly pouch and ileostomy patients) • Discuss the impact on fertility (especially for women) and consider options regarding future fertility such as laparoscopic techniques or delaying surgery until they have had a family • Give informed consent. It is important that patients are empowered to make informed decisions at all stages of their care, for example giving access to information on the outcome and complication rates of the different services can support patients to make a more informed judgement about their care • Optimise the patient's treatment and physical condition (including nutritional assessment) ahead of surgery	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Crohn's & Colitis UK	Guideline	13	20	Notes of the person's views (preferably *preferences and goals*) should also be included in their personalised care plan (as appropriate).	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.

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Crohn's & Colitis UK	Guideline	15	3	This section does not make clear enough to members of the general public what the specific links between bone health and Crohn's Disease are or recommended actions to take. Prolonged corticosteroid use is a risk factor for osteoporosis in Inflammatory Bowel Disease. The BSG IBD guideline recommends patients prescribed a course of steroids should be first assessed for risk of osteoporosis and prescribed vitamin D and calcium supplements as part of their treatment course. Patients on long courses of corticosteroids should be tested regularly (bone densitometry). More general risk factors also include malnutrition, inflammation, smoking and lack of weight-bearing exercise, all of which should be screened for and addressed. We would ask that this recommendation be revised and bought in line with the IBD Standards which states that following diagnosis that all patients should have full assessment of bone health (as well as assessment of their disease, nutritional status, mental health and baseline infection screen) and that this information is recorded in their personalised care plan. In line with good practice and evidence-based approaches (as set out in the Royal College of General Practitioners and Crohn's & Colitis UK IBD toolkit www.rcgp.org.uk/ibd), healthcare professionals should be directed to: • Measure bone mineral density (BMD) to assess fracture risk in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer). • Bone-protective treatment should be started at the onset of glucocorticoid therapy in individuals at high risk of fracture, including some pre-menopausal women and younger men, particularly in individuals with a previous history of fracture or receiving high doses of glucocorticoids.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Crohn's & Colitis UK	Guideline	15	12	This section does not adequately reflect current practice and thinking in relation to supporting those living with Crohn's Disease who wish to conceive or are pregnant. Additional information should include: • The impact of surgery on fertility. For female patients requiring sub-total colectomy and ileostomy, decisions regarding protectomy and ileoanal pouch reconstruction should be discussed because of the potential for impaired fertility. Decisions should be personalised, including use of laparoscopic techniques, and the option of delaying until after completion of the family. • Medications to avoid when trying to conceive (e.g. methotrexate) • The impact and use of medications in pregnancy (e.g. biologics)	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.

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				• The method of delivery (e.g. possible caesarean section for those with active perianal Crohn's Disease, an ileo-anal pouch or vulvul Crohn's disease - multidisciplinary working is key in these circumstances, drawing in the patient and obstetrician to enable shared and informed decision making) • Action to reduce the risk of VTE prophylaxis after a caesarean section/surgery • Treatment that is available to support fertility • Breastfeeding and medication • Increasing folic acid supplements where a person with Crohn's disease has had surgery or are taking certain medications • Neonatal vaccinations after exposure to biologics • Managing a stoma when pregnant • The risks of a child having Crohn's disease (e.g genetics) Crohn's and Colitis UK's advice on pregnancy and fertility can be read here. Research on the transition to motherhood for people with Crohn's and Colitis can be read here.	
Crohn's & Colitis UK	Guideline	17	26	We would strongly urge the committee to revisit the definition and description of Crohn's Disease as currently drafted, including clearer references to complications and extraintestinal manifestations. It would also benefit from the inclusion of a reference to role of self-management and education. https://www.crohnsandcolitis.org.uk/about-inflammatory-bowel-disease/crohns-disease	Thank you for your comment. The context section is only intended to provide a very brief overview of the condition..
Crohn's & Colitis UK	Guideline	18	1-2	We wish to query *'Smoking and genetic predisposition are 2 important factors that are likely to play a role'.* Crohn's & Colitis UK usually refer to environmental factors in broader terms: • the genes you are born with, • plus an abnormal reaction of your immune system to certain bacteria in your intestines, • along with an unknown trigger that could include viruses, bacteria, diet, smoking, stress or something else in the environment.	Thank you for your comment. The context section is only intended to provide a very brief overview of the condition.
Crohn's & Colitis UK	Guideline	18	1	This figure is not attributable to Crohn's & Colitis UK	Thank you for your comment. This figure was taken from CG152 Crohn's disease: management full guideline. We have corrected this error.
Crohn's & Colitis UK	Guideline	18	4	We would ask the committee to revisit the use of the term 'attacks', in favour of "flares" and/or "relapse".	Thank you for your comment. We have changed the wording to relapse.

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Crohn's & Colitis UK	Guideline	18	11	We would ask the committee to review the references to nutrition - as currently drafted, these are confusing and potentially misleading. Should '*attention to nutrition'* be enteral nutrition? Crohn's and Colitis UK's booklet on food and diet can be read here.	Thank you for your comment. This should be "attention to nutrition" because the statement refers to the patient's overall nutritional status and nutritional intake as important contributing factors to their health and not just enteral nutrition therapy.
Department of Health and Social Care		General	General	I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding this consultation.	Thank you for your comment.
Intensive Care Society	Guideline	General	General	This document, especially in the section relating to post-surgery, could include a statement on when to discuss patients to Critical Care.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Janssen UK	Guideline	12	14	Ustekinumab is not referred to in section 1.3 Maintaining remission in Crohn's disease. The guideline currently states: "See recommendation 1.2.16 for when to continue infliximab or adalimumab during remission". There is no mention of the NICE TA456 recommendation for ustekinumab which could cause confusion. We suggest adding the NICE TA456 recommendations for ustekinumab use as detailed below: Ustekinumab should be given until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed in accordance with NICE's recommendations for infliximab and adalimumab for the treatment of Crohn's disease to see whether treatment should continue. Treatment with ustekinumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with ustekinumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.	Thank you for your comment. TA456 (ustekinemab) has not been moved to the static list and therefore could be subject to future updates by the Technology Appraisals programme. In these cases, the current NICE approach is to insert a link to cross-refer to the TA so that if the TA is updated and the recommendations change, the guideline will refer readers to the most up to date recommendations.
Janssen	Guideline	8-10	Page	We suggest that there should be consistency in the presentation of biologic recommendations and	Thank you for your comment. This part of

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UK			8 line 9 to page 10 line 27	clarity in terms of how biologics are ordered within the guideline. Infliximab, adalimumab and ustekinumab are all recommended for 1st line use but the layout of biologic recommendations in chronological order does not make this clear. We suggest that the ordering of biologic recommendations is aligned to treatment line, by explicitly stating what treatment options are available at 1st line biologic and subsequent stages in the treatment pathway. This would allow healthcare professionals to recognise the work NICE have undertaken in thoroughly reviewing these technologies at each stage of the pathway.	the guideline was out of the scope of this update and therefore we are unable to make changes to it. The technology appraisal TA187 for infliximab and adalimumab has been moved to the 'static list' and will not be updated in the future as a technology appraisal. This means the recommendations from the TA can be either incorporated or updated as part ofa relevant NICE guideline. TA456 (ustekinemab) and TA352 (vedolizumab) have not been moved to the static list and therefore they could be subject to future updates by the Technology Appraisals programme. In these cases, a link has been inserted to cross-refer to the TA so that if the TA is updated and the recommendations change, the guideline will refer readers to the most up to date recommendations.
Janssen UK	Guideline	General	General	The Guideline does not make it clear that moderate to severe patients can have multiple biologic treatments, as per TA456 and TA352, which could lead to sub-optimal patient outcomes. We suggest the following sentences could be added to section 1.2: For patients who have had an inadequate response with, lost response to or were intolerant to conventional therapy (or have medical contraindications to such therapies) a biological therapy should be considered. For patients who have had an inadequate response with, lost response to or were intolerant to a biologic therapy (or the therapy is medically contraindicated) then a subsequent biological therapy should be considered.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.

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				The 2019 draft guideline provides an opportunity for NICE to reiterate clinical management options that have become available since 2010, with the aim of encouraging better outcomes if initial therapies prove ineffective. We suggest the following sentence could be added to section 1.2: Patients should be routinely assessed for clinical response, and for patients who have had an inadequate response with, lost response to or were intolerant to a biological therapy (or the therapy is medically contraindicated) then a subsequent biological therapy should be considered.	
Janssen UK	Guideline	General	General	There appears to be confusion on the definition of mild, moderate and severe disease in the guidelines and what populations these refer to. It would be useful to make it clear at the start of the guideline what population is being referred to and how the severity of the population has been categorised (what scales/scores have been used).	Thank you. This update covered all people who have had surgery for Crohn's disease. It was not restricted by disease severity. The classification of disease severity was outside the scope of this update. We have passed your comment to the surveillance team for consideration at future updates.
Janssen UK	Guideline	General	General	A summary table detailing what treatments are recommended for which populations could be added at the end of the document to improve the clarity of the guideline recommendations.	Thank you for your comment. This is outside the remit of this partial update.The interactive flowchart available at the NICE website directs the reader to all available guidance on Crohn's disease.
Napp Pharmaceuticals Limited	Guideline	Page8	Line 4	We note that NICE has referred to TA187 Infliximab and adalimumab for the treatment of Crohn's disease, and have included statements from the guidance 1.2.11 etc. We suggest that it would help the NHS to include also from the above guidance point 1.2: *(Treatment as described in 1.1 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.).* From February 2015 biosimilars of infliximab have been available, the NHS list price as shown in the BNF for Remsima® is £377.66 per 100mg vial. (shown in Table35) but this does not reflect the true price paid today.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. In accordance with our methods manual, public list prices for medicines are used in the reference-case analysis. Analyses based on price reductions for the NHS will be considered when the reduced prices are

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				The actual price paid by the NHS is much lower due to the procurement tender process. The real discounted price is in the range of 75% to 90% of the originator infliximab product Remicade® £419.62 per 100mg vial. We would encourage the ERG to review the price inputs for any calculation of ICERs to ensure that the correct discounted prices are applied for infliximab.	transparent and can be consistently available across the NHS. We checked for nationally available price reductions for infliximab in eMIT but no information was available and therefore the list price from the BNF was used.
Napp Pharmaceuticals Limited	ERG review	Page 38 and Page 238	Line10-17 and Line15-18	In relation to the above we note that the ERG have applied discounts of 25%, 50% and 75% to the cost of infliximab and adalimumab. Note that this is different to the range suggested above (75%-90%) for biosimilar infliximab which if used should give a more realistic estimate of cost-effectiveness.	Thank you for your comment. In accordance with our methods manual, public list prices for medicines are used in the reference-case analysis. Analyses based on price reductions for the NHS will be considered when the reduced prices are transparent and can be consistently available across the NHS. We checked for nationally available price reductions for infliximab in eMIT but no information was available and therefore the list price from the BNF was used. Discounts of 25%, 50% and 75% for biosimilars were only considered in an exploratory analysis.
Napp Pharmaceuticals Limited		Page 38	Line 19-27	The committee suggested that there may be cost savings related to not using high cost drugs (biologics). However, with discounts of 75%-90% on the NHS list price of the originator, biosimilar infliximab is now a much lower priced drug comparable to many every day treatments in other therapy areas.	Thank you for your comment. In accordance with our methods manual, public list prices for medicines are used in the reference-case analysis. Analyses based on price reductions for the NHS will be considered when the reduced prices are transparent and can be consistently available across the NHS. We checked for nationally available price reductions for infliximab in eMIT but no information was available and therefore the list price from the BNF was used. Discounts of 25%, 50% and 75% for biosimilars were only considered in an exploratory analysis.
[NHS England]	1.4.1	12	17-20	3m of metronidazole and azathioprine recommended. Doesn't mention what monitoring is required for this combination, and as it is off-licence I am not sure what the correct monitoring should be. Presumably this should be prescribed and monitored under the secondary care	Thank you for your comment. A recommendation to monitor azathioprine and metronidazole is now included. The

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				specialist (not stated here)?	recommendation reads: "Monitor the effects of azathioprine and metronidazole as advised in the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in people taking azathioprine even if they have normal TPMT activity (see also recommendation 1.2.11)."
[NHS England]		General	General	Does it make any difference if the resection is not clear when histology is reported? This guidance suggests it does not.	Thank you for your comment. It makes an important difference. This update only covers post-surgical maintenance of remission. If patients are not in remission (ie they still have active disease, for example on histology) then they are not covered by these recommendations. The committee specified the population in the recommendations as people who have had complete macroscopic resection and have no residual active disease.
Primary Care Society for Gastroenterology	Guideline	5	20	Budesonide may be used as an alternative to prednisolone for patients with mild to moderate Crohn's disease affecting the ileum or ascending colon https://bnf.nice.org.uk/drug/budesonide.html#indicationsAndDoses	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Primary Care Society for Gastroenterology	Guideline	5	24	EEN may also be used in adults World J Gastroenterol. 2013 Nov 21; 19(43): 7652–7660. Published online 2013 Nov 21. doi: 10.3748/wjg.v19.i43.7652. This is also stated in the current BSG IBD guidelines Gut 2011;60:571e607. doi:10.1136/gut.2010.224154	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. We have passed your comment on to the surveillance team for consideration in future updates.
Primary Care Society for Gastroenterology	Guideline	6	9	BSG IBD Guidance 2011 states "There is no evidence that 5-ASA is superior to placebo for the maintenance of medically induced remission" Gut 2011;60:571e607. doi:10.1136/gut.2010.224154	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.

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Primary Care Society for Gastroenterology	Guideline	7	5 & 19	BSG IBD Guidance 2011 states "any patient who has a severe relapse or frequently relapsing disease < those who require two or more corticosteroid courses within a 12 month period < those whose disease relapses as the dose of steroid is reduced below 15 mg < relapse within 6 weeks of stopping corticosteroids"	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Primary Care Society for Gastroenterology	Guideline	General	General	The new BSG IBD Guidance has been submitted for publication. This should be published in the Spring of 2019. It would seem sensible to await this publication so that the NICE Guidance can be updates to reflect the detailed and comprehensive work that has gone into this document, and to ensure that proper alignment of the recommendations can take place	**NICE is aware of the forthcoming BSG IBD guideline. NICE and the BSG have met to discuss the synergies and overlaps in the 2 organisations' portfolios for gastroenterology topics. For this particular guideline the update covers only the maintenance of remission following surgery in Crohn's disease. Following the publication of the BSG guideline NICE will consider the impact on the Crohn's disease guideline.** This guideline update only reviewed evidence on pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. This area was prioritised for update because new evidence was identified that could have an impact on recommendations.
Primary Care Society for Gastroenterology	Guidance	General	General	The review lacks clarity on the diagnostic pathway, and communication between primary and secondary care. It would more complete if this could be added.	Thank you for your comment. This part of the guideline was out of the scope of this update updated and therefore we are unable to make changes to it.
Primary Care Society for Gastroenterology	Guidance	General	General	Identification and initial management of flare is also missing. Primary care and patients would benefit greatly from having a simple algorithm for this, as it can be difficult to recognise when a flare is occurring, when to use self-care, and when to seek further advice. A care plan provided by secondary care to primary care and the patient can form an essential part of this.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Primary Care	Guidance	General	General	The role of the clinical nurse specialist/IBD nurse does not have a high enough profile in this review. Areas that have a high proportion of IBD nurses (https://www.nice.org.uk/guidance/qs81)	Thank you for your comment. This part of

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Society for Gastroenterology				often have a lower admission rate and shorter length of stay.	the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Royal College of General Practitioners	Guideline	5	20	Budesonide may be used as an alternative to prednisolone for patients with mild to moderate Crohn's disease affecting the ileum or ascending colon https://bnf.nice.org.uk/drug/budesonide.html#indicationsAndDoses	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Royal College of General Practitioners	Guideline	5	24	EEN may also be used in adults World J Gastroenterol. 2013 Nov 21; 19(43): 7652–7660. Published online 2013 Nov 21. doi: 10.3748/wjg.v19.i43.7652. This is also stated in the current BSG IBD guidelines Gut 2011;60:571e607. doi:10.1136/gut.2010.224154	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. We have passed your comment on to the surveillance team for consideration in future updates.
Royal College of General Practitioners	Guideline	6	9	BSG IBD Guidance 2011 states "There is no evidence that 5-ASA is superior to placebo for the maintenance of medically induced remission" Gut 2011;60:571e607. doi:10.1136/gut.2010.224154	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Royal College of General Practitioners	Guideline	7	5 & 19	BSG IBD Guidance 2011 states "any patient who has a severe relapse or frequently relapsing disease < those who require two or more corticosteroid courses within a 12 month period < those whose disease relapses as the dose of steroid is reduced below 15 mg < relapse within 6 weeks of stopping corticosteroids"	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Royal College of General Practitioners	Guideline	General	General	The new BSG IBD Guidance has been submitted for publication. This should be published in the Spring of 2019. It would seem sensible to await this publication so that the NICE Guidance can be updates to reflect the detailed and comprehensive work that has gone into this document, and to ensure that proper alignment of the recommendations can take place	**NICE is aware of the forthcoming BSG IBD guideline. NICE and the BSG have met to discuss the synergies and overlaps in the 2 organisations' portfolios for gastroenterology topics. For this particular guideline the update covers only the maintenance of remission following surgery in Crohn's disease. Following the publication of**

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					the BSG guideline NICE will consider the impact on the Crohn's disease guideline. This guideline update only reviewed evidence on pharmacological interventions and enteral nutrition for post-surgical maintenance of remission. This area was prioritised for update because new evidence was identified that could have an impact on recommendations.
Royal College of General Practitioners	Guidance	General	General	The review lacks clarity on the diagnostic pathway, and communication between primary and secondary care. It would more complete if this could be added.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Royal College of General Practitioners	Guidance	General	General	Identification and initial management of flare is also missing. Primary care and patients would benefit greatly from having a simple algorithm for this, as it can be difficult to recognise when a flare is occurring, when to use self-care, and when to seek further advice. A care plan provided by secondary care to primary care and the patient can form an essential part of this.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
Royal College of General Practitioners	Guidance	General	General	The role of the clinical nurse specialist/IBD nurse does not have a high enough profile in this review. Areas that have a high proportion of IBD nurses (https://www.nice.org.uk/guidance/qs81) often have a lower admission rate and shorter length of stay.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
[Royal College of Nursing]	General	General	General	The Royal College of Nursing (RCN) welcomes proposals to update the NICE Crohn's Disease Management guideline. The RCN invited members who care for people with this condition to review the draft document and comment on its behalf. The comments below reflect the views of our reviewers.	Thank you for your comments.
[Royal College of Nursing]	Guideline	10	25	The NICE Technology Appraisal should read the same for Vedolizumab as for Ustekinumab in regard to cost: Ustekinumab Guidance Recommendation 1.1: The choice of treatment between ustekinumab or another biological therapy should be made on an individual basis after discussion between the	Thank you for your comment. This guideline update only considered evidence on treatments for post-surgical maintenance of remission. As part of the current update, we are unable to make

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				patient and their clinician about the advantages and disadvantages of the treatments available. If more than one treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).	changes to other recommendations where the evidence has not been reviewed. The guideline has been refreshed to include cross-references to other relevant NICE guidance. TA456 (ustekinemab) and TA352 (vedolizumab) are active technology appraisals that could be updated in the future, therefore a link has been inserted to cross-refer to the technology appraisal to ensure that the most up to date recommendations are available..
[Royal College of Nursing]	Guideline	12	16	Section 1.4: We are concerned that the recommendations recognise the need for maintenance after surgery but considers offering Azathioprine combination with up to three months' postoperative metronidazole. This seems discriminatory and unfair; as the offers seems to be considering those patients who tolerate Azathioprine. Surely provision needs to be made for all patients rather than a select group based on drug tolerance. Prevention of recurrence should be a priority with Crohn's disease as recurrent surgeries, complications with active disease requiring drug escalation and poor quality of life will surely negate any perceived cost benefits.	Thank you for your comment. The committee discussed that not all people who undergo ileocolonic resection require or choose to receive treatment to maintain remission. The recommendations in Section 1.4 identify treatment options that can be considered but no treatment remains an option. Section 1.4 also identifies treatments that the committee felt should not be used to maintain remission because in the case of budesonide, the treatment is not effective and in the case of the mercaptopurine and the biolgoics, the cost-effectiveness analysis showed that the incremental health benefits did not justify the additional costs. This analysis took into account not only the cost of the drugs to maintain remission, but also the cost of downstream events (relapses, the need for further treatment to induce remission and surgery).
Royal College of Paediatrics and Child Health				The reviewer was pleased with the documents	Thank you for your comment.

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Royal College of Physicians		General	General	We would like to endorse the responses submitted by the British Society of Gastroenterology (BSG).	Thank you for your comment.
South Worcestershire CCG		8-10	General	This section relates to use of biologic therapies adalimumab, infliximab, ustekinumab and vedolizumab. There is a lack of clarity in related technology appraisals with regard to: • the sequential use of these agents (including how many?). If no advice in relation to sequential use is to be provided then it would be helpful if the guideline acknowledges local pathways of care that might better inform use of biologics. • use of all agents for fistulising disease. Whilst infliximab is the only agent that relates to fistulising disease within the indication, indications for other agents are more ambiguous, with some citing relevant evidence but not necessarily excluding fistulising disease. It would be more helpful if the technology appraisal recommendations for vedolizumab and ustekinumab were included in this section rather than a link; this is currently inconsistent as the recommendations for adalimumab and infliximab are included.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. We have passed your comment on to the surveillance team for consideration in future updates.
South Worcestershire CCG		9	5	Limited advice is provided with regard to add-on treatment with biologic therapies; the extract relates only to infliximab and adalimumab and discusses combination therapy (with immunosuppressants) at the outset, it does not relate to add-on therapy should efficacy wane at a later stage. There is no reference to either combination therapy or add-on therapy with ustekinumab or vedolizumab, which would be helpful if included.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. We have passed your comment on to the surveillance team for consideration in future updates.
South Worcestershire CCG		9	20	Further definition of "active" disease would better inform practice (see also comment 5).	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.
South Worcestershire CCG		General	General	The guideline would benefit from further guidance specifically in relation to management of fistulising disease, an often cited circumstance warranting further biologic intervention.	Thank you. The management of fistulating disease is outside the scope of this guideline.
South Worcestershire CCG		10	28	Further advice is required in relation to maintaining remission with biologic agents. Section 1.2.16 alludes to this but does not meet with clinician expectation, particularly in circumstances where patients are unable to take other immunosuppressants. Local clinicians have suggested that a "trial withdrawal" may not be appropriate for the following patient groups: - Small bowel disease (for whom surgery is not an option; such patients are largely known at the outset/initiation) - Short duration of remission (ideally require at least 12 months and possibly up to 3-4 years) - Lack of available alternative options either biologics or DMARDs (specifically azathioprine or mercaptopurine) due to either prior lack of response or contra-indication - Risk of antibody development if treatment stopped and subsequent lack of response	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it.

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				when restarted - Disease severity/history concern	
South Worcestershire CCG		13	3	It is common practice in Worcestershire to continue use of biologics after surgical resection; this new NICE recommendation "not to offer biologics to maintain remission after complete macroscopic resection of ileocolonic Crohn's disease" will therefore have a significant impact and should be recognised in a summary table at the end of the guideline outlining all new 2019 changes. It would also be helpful to advise: i. when biologic treatment should stop in relation to the surgical intervention ii. what maintenance treatment should be offered post CMR in patients unable to take azathioprine iii. whether there are any circumstances when a biologic may be appropriate (see also comment 3 above) including other types of surgical intervention (non-CMR of ileocolonic CD) iv. what circumstances would support a patient re-starting biological treatment post-surgery and where in the pathway a patient would sit; do they reconvene in the same place ie. as a second line biologic treatment or do they recommence as a 1st line treatment as it could be considered new disease?	Thank you for your comment. The tables at the end of the guideline that you refer to is a summary of edits made to recommendations (ie that have been deleted or amended). The previous (2012) guideline did not make any recommendations about the use of biologics to maintain remission after surgery. This update is the first time NICE has reviewed the evidence for the use of biologics in the post-surgical setting and so this is not included in the tables. The update covers only the maintenance of remission after surgery. It does not cover patients who have surgery and whose disease is not in remission. Section 1.2 of the guideline makes recommendations for inducing remission in people with active disease. i) Guidance on when biologic treatment should stop in relation to surgery is covered in 1.2.12 for infliximab and adalimumab and in technology appraisals TA456 (ustekinumab) and TA342 (vedolizumab). ii) The guideline does not make any specific recommendations about what treatment should be considered for post-surgical maintenance of remission in people who are unable to tolerate azathioprine. iii) There was insufficient evidence of clinical and cost effectiveness to define any specific circumstances or populations when a biologic could be recommended for post-surgical maintenance of remission.

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					iv) If a patient relapses following surgery, their disease is no longer in remission and the recommendations for inducing remission (1.2 of the guideline) would apply.
Surrey Downs Clinical Commissioning Group	Guideline	10	1.2.21	To include relevant sections of guidance from NICE TA (as has been done for infliximab and adalimumab; 1.2.12 to 1.2.20)	Thank you for your comment. The technology appraisal TA187 for infliximab and adalimumab has been moved to the 'static list' and will not be updated in the future as a technology appraisal. This means the recommendations from the TA can be either incorporated or updated as part ofa relevant NICE guideline. TA456 (ustekinemab) and TA352 (vedolizumab) have not been moved to the static list and therefore they could be subject to future updates by the Technology Appraisals programme. In these cases, a link has been inserted to cross-refer to the TA so that if the TA is updated and the recommendations change, the guideline will refer readers to the most up to date recommendations.
Surrey Downs Clinical Commissioning Group	Guideline	10	1.2.22	To include relevant sections of guidance from NICE TA (as has been done for infliximab and adalimumab; 1.2.12 to 1.2.20)	Thank you for your comment. The technology appraisal TA187 for infliximab and adalimumab has been moved to the 'static list' and will not be updated in the future as a technology appraisal. This means the recommendations from the TA can be either incorporated or updated as part ofa relevant NICE guideline. TA456 (ustekinemab) and TA352 (vedolizumab) have not been moved to the static list and therefore they could be subject to future updates by the Technology Appraisals programme. In these cases, a link has been inserted to cross-refer to the TA so that if the TA is updated and the

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					recommendations change, the guideline will refer readers to the most up to date recommendations.
Tillotts Pharma UK Ltd	Guideline 1.2.3 Consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period for people:	6	General	**Recommendations** Our first recommendation would be to follow the ECCO guidance and subgroup patients further by severity (mild and moderate disease). ECCO recommends budesonide first line for mild disease and gives patients a preference option for moderate disease. If it is not possible to directly replicate this format we recommend the statement should read: 1.2.3 Consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period for people: • who have one or more of distal ileal, ileocaecal or right-sided colonic disease and • if conventional glucocorticosteroids are contraindicated, or if the person declines or cannot tolerate them. Explain that budesonide, a locally acting steroid, causes significantly fewer side effects than conventional glucocorticosteroids. **Our concerns** We are aware the wording of the recommendation 1.2.3 has been altered in this review and we do not believe this reflects the conclusion of the Cochrane review (Rezaie *et al* 2015) and NICE analysis (appendix G). In both of these reviews no significant difference was observed between the efficacy of conventional glucocorticosteroids and budesonide in patients with terminal ileal, or ileo-colonic disease, however a difference was observed with patients with a more severe presentation, which is already ruled out as a treatment option (1.2.5 Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations). Based on this it does not appear correct to conclude budesonide 'is' less effective than conventional steroids as the patients are already stratified to those with ileal, ileocaecal or right-sided colonic disease where no difference was observed.	Thank you for your comment. This part of the guideline was out of the scope of this update and therefore we are unable to make changes to it. Recommendation 1.2.3 was edited into an active recommendation to adhere to NICE editorial style. The meaning of the recommendation remains as the original wording.
Tillotts Pharma UK Ltd	Evidence review	202	Table 34	There are a number of errors in the cost calculations. For all mesalazine preparations, the cost per day is incorrect. The cost per day should be calculated as follows: Pack price divided by number of doses = cost per tablet Cost per tablet multiplied by number of tablets required to achieve average daily dose = cost per day Example calculation for Asacol 400mg Pack price (£27.45) divided by number of doses (84) = cost per tablet (£0.33) Cost per tablet (£0.33) multiplied by number of tablets required to achieve average daily dose (6) = cost per day (£1.96)	Thank you for your comment. The daily cost of mesalazine formulations was checked and has been corrected in the economic model and the evidence report. The change to the drug cost resulted in the mesalazine strategy being more expensive than the no treatment strategy. In the scenario where it is assumed there is no azathioprine and no metronidazole in the decision space, the probability that mesalazine is cost effective has decreased. Results have been updated in the evidence report but this change did not affect the overall guideline

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				The costs per day for the mesalazines should be as follows: Asacol 400mg £1.96 Octasa 400mg £1.11 Asacol 800mg £1.96 Octasa 800mg £1.35 Please consider these errors and whether they have consequences in other calculations within the evidence review and hence the draft guideline	recommendations.
[University of Central Lancashire]	Evidence	166	General	We are currently very familiar with this evidence, having authored previous Cochrane reviews on this topic cited in the 2012 and 2016 guidance. We are currently completing our Network Meta-analysis (NMA). In giving this response, we have consulted with editors and managing editors of the team, methodologists and a colleague who is a lead for the regional CLAHRC with specific expertise in NMA. The authors have MET+AZA (metronidazole and azathioprine) versus MET (metronidazole) from the DHeans 2008 study in the network and there are many reasons we believe this is not valid • We would have thought it should be MET+AZA vs MET+Placebo. As such, it would disconnect MET+AZA from the network in a separate sub-network. • Probably far more important, clinically it is worth stating that in most studies Metronidazole is an excluded concomitant therapy. In this study it must be noted, this is not a randomised therapy but a concomitant therapy given for 3 months to both groups – which suggests it's not clinically a valid comparator across the rest of the network. This is different to studies which randomise metronidazole which are obviously valid. • Effectively DHeans 2008 doesn't actually randomise patients to MET+AZA or MET+Placebo, but to AZA vs Placebo with a concurrent medication of MET. I assume that the argument you have made is you think effectively it is a combined treatment (MET+AZA). We can't remember an occasion where we have seen that previously, with people tending to compare the randomised interventions and noting other concurrent interventions that may have had an effect to explain unusual results. In addition, they only get MET+AZA for 3 months and AZA alone for another 9 months (total of 12 months), so its likely that the effect of the combined intervention would be at 3 months and at 12 months it would be the AZA. For all these reasons, we believe the Dheans study should be removed from the network and only reported in direct comparisons.	Thank you for your comment. Prior to carrying out the network meta-analysis, the committee advised that treatment with metronidazole is generally only given for up to 3 months but that it is possible the drug could have a lasting effect at 12 months. The committee also discussed that the combination of metronidazole + azathioprine could have a synergistic effect and therefore felt it was important to consider this combination as a separate node in the network meta-analysis. This approach was taken consistently across the network. Removing the D'Haens study would not disconnect the network as there is another study comparing MET+AZA versus AZA.
[University of Central Lancashire]	Guideline	12	16	The first recommendation 1.4.1, a new recommendation, is based on the dheans study only and as above we feel it is clinically inappropriate to include this study in the network meta-analysis. If it is considered purely as a direct comparison, we simply cannot see the justification for the	Thank you for your comments. The committee took into account the results of the pairwise analyses, network meta-analyses and cost-effectiveness analysis in

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				recommendation as it is not supported by any evidence: • This is just one study at just 2 hospitals in 1 country with just 81 patients participating, just 1 year follow up and a high 25% attrition for such a short study. • The specific outcome measures did show a small statistical difference in rates of endoscopic remission, but no impact on clinical remission was found with half of patients in both groups in clinical relapse (evidence page 133). • The GRADE rating is low, particularly noting risk of bias and imprecision – to make a primary recommendation in such a situation is concerning. • As touched on above, we believe it is simply invalid to describe or recommend the results of this study as demonstrating that metronidazole and AZA is effective. Indeed, Metronidazole is a concomitant therapy that is excluded in most other studies. It was not randomised and given for 3 months. Surely ,the only conclusion the committee can and should make is that 'in patients already taking metronidazole, AZA has some impact on endoscopic remission. We believe this should be removed completely and moved to the suggested research section and only if such studies that randomise to placebo or combination therapy are completed can this be added.	making recommendations. The current review identified 2 main studies that assessed the use of azathioprine in combination with 3 months of metronidazole: D'Haens (2008) and Manosa (2013). The network meta-analysis showed a significant benefit for azathioprine + metronidazole compared to placebo for the outcome endoscopic relapse. The committee prioritised endoscopic relapse as the most important outcome because it is an objective measure of disease and because the goal of treatment in Crohn's disease has shifted from symptom relief alone towards mucosal healing. For both endoscopic and clinical relapse, all the treatments that ranked ahead of azathioprine + metronidazole in the network meta-analyses included a biologic agent. The economic model concluded that regimens containing biologics were not cost effective and the committee agreed they could not be recommended for post-surgical maintenance of remission.
[University of Central Lancashire]	Guideline	13	1	Recommendation 1.4.2 We do not see evidence that in anyway supports this recommendation. We are mindful these are a widely used therapy; however this does not mean that their inclusion is supported. In fact, the network meta-analysis which has the ability to clarify this issue has not shown any role for AZA in clinical remission (evidence page 166 clinical remission and page 174 endoscopic remission). As per our previous Cochrane review in 2014, the indivual studies and meta-analysis find limited evidence for AZA. There are no studies against placebo and the analysis on page 130 of the evidence shows no overall difference and 1 study favouring mesalazine and 1 AZA. There is no difference in endoscopic remission. We do not think AZA should be recommended, based on the evidence and considering the high rate of none tolerance. However, if included, as per our response below, we believe the evidence	Thank you for your comments. Although azathioprine did not show a statistically significant benefit compared to placebo in the network meta-analyses for clinical and endoscopic relapse, the point estimates for the hazard ratios for both outcomes favoured azathioprine. Taking into account uncertainty around the treatment effects for all comparators in the cost-effectiveness scenario analysis without metronidazole, azathioprine generated more health benefits in terms of total QALYs and lower total costs compared to no treatment, budesonide and mesalazine and had a

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				suggests they should be recommended after 5-ASA (5-aminosalacyclic acid / mesalazine) As the committee are aware, the evidence that exists in both the NMA and the individual analysis actually supports Mercaptopurine, although this is always limited, but for cost reasons has been removed. We understand and support this, but think this should be explicit in the guidance.	72% proability of being cost effective at a threshold of £20,000/QALY. This same scenario analysis showed that although mercaptopurine was more effective than azathioprine at reducing endoscopic relapse, it is not cost effective at its current price. This is stated explicitly in the rationale and impact section of the guideline. The evidence from the network meta-analyses did not show a clear benefit for mesalazine compared to placebo for endoscopic relapse and the economic analysis showed mesalazine is unlikely to be cost effective. For these reasons, the 2012 recommendation was removed and the committee agreed not to recommend aminosalicylates, including mesalazine.
[University of Central Lancashire]	Guideline	16	26-29	This statement and the statement in table 1 on page 20 state the removal of 5-ASA. Firstly, this was re-added in 2016 and this seems to be ignored. The rationale that 'the experience of the committee' is that these aren't effective and in the table 'there is newer evidence supporting 5-ASA' are very concerning. Experience always seem an undesirable proxy for evidence, Indeed, there is 50 years experience with 5-ASA and their safety is well recognised. Their low cost is also vital to consider and given that there is no evidence for AZA (above) and 6MP and biologics too expensive, to ignore them	Thank you for your comments. NICE guidelines make evidence-based recommendations informed by the expertise of the guideline committee. The evidence from the network meta-analyses did not show a clear benefit for mesalazine compared to placebo for endoscopic relapse and the economic analysis showed mesalazine is unlikely to be cost effective. For these reasons, the 2012

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				without considering evidence seems concerning. Indeed, the rationale 'evidence supports AZA' is not what the evidence states. We have already referred to the forest plots and given there is no difference in endoscopic relapse, no overall difference in clinical relapse and most concerning on page 131 the withdrawals in AZA groups is twice as likely than in mesalazine groups (just not statistically significant touching line of no effect), this statement is factually wrong. However, these points ignore the fact that the analysis presented has been selective and introduced bias. We are completing our own Cochrane NMA and update of our 5-ASA review currently. We cannot see why relapse data from the mcelod study is not included in the NMA on 162. It is missing from the evidence table on page 105, but included in safety analysis so we suspect this is a mistake, but with significant impact. Also, the network includes the yoshida study which is stated as infilimab and Mez vs mesalzine. Similar to our comments on the dhenas 2008 study, this is not appropriate as Mesalazine was not a randomised therapy in this trial and instead a concomitant therapy, Including this in the network invalidates the network and biases the data. Indeed once mcloed is included and yoshida removed from the network in terms of contributing Mesalazine data, as it is in our NMA and review, the results shift to find Mesalazine as the second effective therapy in the network after Adalimumab. We would invite the team to strongly consider these apparent mistakes and biases and rerun the analysis. We are happy to share our soon to be published Cochrane works. We believe that 5-ASA should be a recommendation and when considering safety, cost and efficacy, we think it should be ranked first, given the QUALYs for the top ranked Adalimumab and 6MP are not appropriate. This is obviously a Committee decision but given the other two recommended therapies are based on flawed interpretation low quality data (met and aza) and no evidence of effectiveness (AZA), this must be considered.	recommendation was removed and the committee agreed not to recommend aminosalicylates, including mesalazine. The McLeod 1995 study was included in the network meta-analysis for clinical relapse but was not included in the network meta-analysis for endoscopic relapse because the secondary endpoint (total recurrence) did not meet the inclusion criteria. In the McLeod 1995 study, total recurrence was defined as the presence of endoscopic or radiological evidence and included both asymptomatic and symptomatic patients. For endoscopic evaluation, the study did not use the Rutgeerts score, which was specified in the protocol. The committee agreed that all concomitant therapy should be classified as combination therapy, due to potential synergistic effects of treatments for maintaining remission after surgery. This was consistent for all studies included in the guideline update. For this reason, infliximab with mesalazine concomitant therapy (Yoshida 2012) was considered as combination therapy.
[University of Central Lancashire]	General	General	General	Azathioprine has always been noted to have high withdrawal rates. Our recent NMA found a significant number of pancreatitis cases in AZA patients compared to all other interventions. We reached out to colleagues on the medical induced CD remission team and managed to consider 30 RCTs in full. These found an incidence of pancreatitis in AZA of 1.8% (12 months – 36 months study length) vs 0.09% in all other interventions as well as placebo. This agrees with a number of observational large cohort studies published and is not currently noted in any versions of the NICE guidance, AGA, BSG, ECCO and in the BNF is noted as rare (less than 1%) which is obviously wrong.	Thank you. The protocol defined withdrawal due to adverse events as an outcome of interest for the review. There was considerable uncertainty in the results of the network meta-analysis for withdrawal due to adverse events, as suggested by the wide credible intervals for many of the treatments. The committee did not specify individual adverse events and we did not

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				We are reporting this to the IBD journal currently and presenting this as major international meetings, but given where AZA sits in the current recommendations, we feel the committee need to consider this. Many rare serious adverse events are well discussed for AZA but for some reason pancreatitis seems to be missing.	specifically search for data on pancreatitis. Due to concerns raised by stakeholders about potential adverse effects, the committee agreed to add a new recommendation to reinforce the need for monitoring in people who are taking azathioprine: "1.4.3 Monitor the effects of azathioprine and metronidazole as advised in the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in people taking azathioprine even if they have normal TPMT activity (see also recommendation 1.2.11)" We look forward to reading the results of your analysis when it is published and will flag this as an area of potential new evidence with our surveillance team.