NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

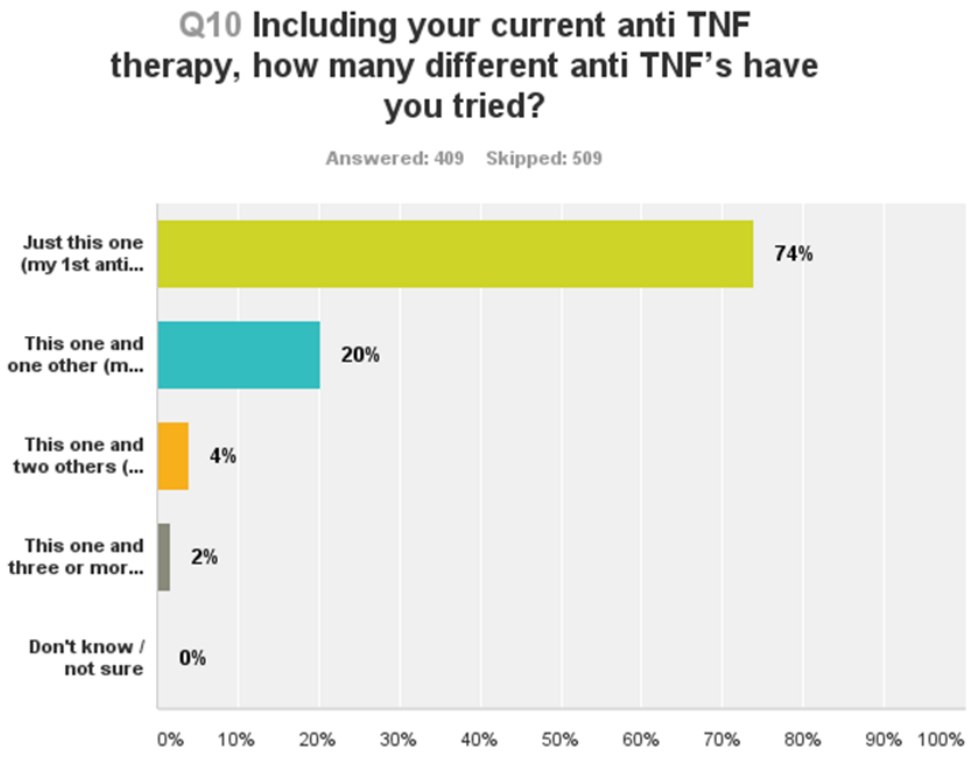
Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

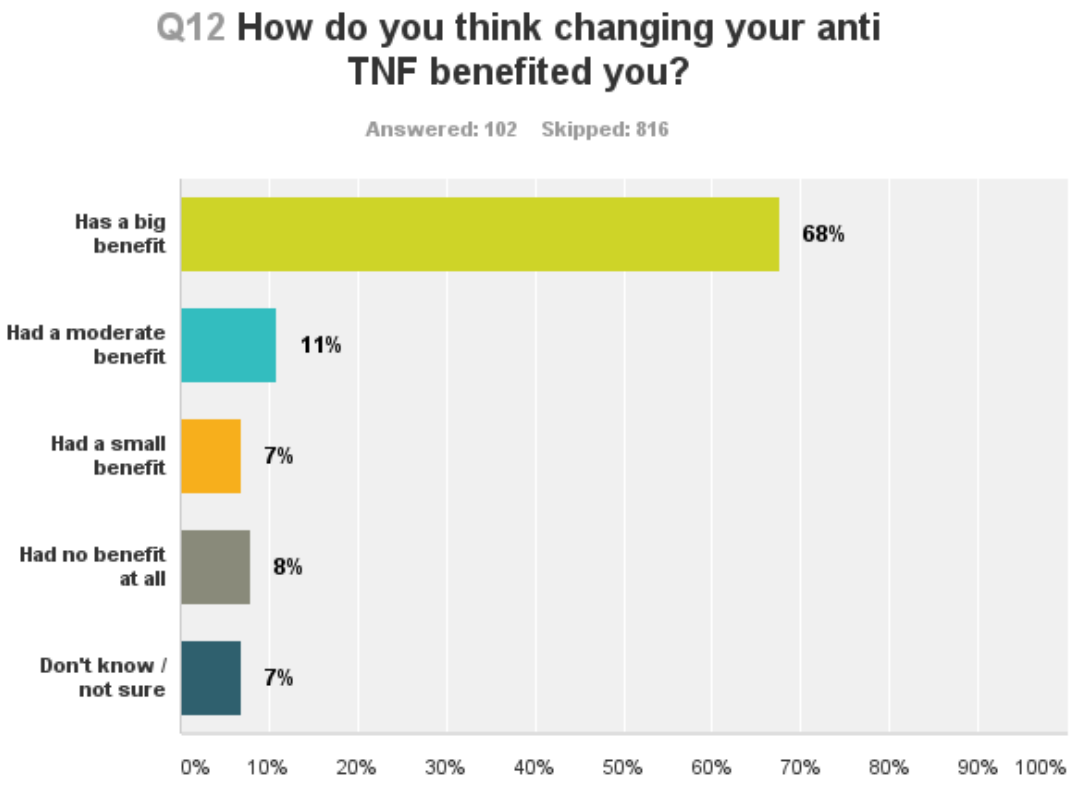
Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
National Ankylosing Spondylitis Society	**Representing the views of people in England with AS and axial spondyloarthritis** In order to fully represent the views of patients with regard to the ACD, NASS conducted a survey of people with ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis living in England. **Adalimumab, certolizumab pegol, etanercept and golimumab are recommended as treatment options for active ankylosing spondylitis (AS)** NASS is happy to see that adalimumab, certolizumab pegol, etanercept and golimumab are recommended as treatment options for active ankylosing spondylitis (AS) in the ACD. 93% of people in the NASS survey were very or quite satisfied with this decision.	Comment noted. No action required.
	Adalimumab, certolizumab pegol and etanercept are recommended as treatment options for non-radiographic axial spondyloarthritis NASS is additionally very pleased to see that the Appraisal Committee has also recommended adalimumab, certolizumab pegol and etanercept as treatment options for non-radiographic axial spondyloarthritis. We know that this will make a very big difference to people living with non-radiographic axial spondyloarthritis who are either unable to take anti inflammatories or are not getting sufficient effect from this class of drugs. In the NASS survey, 94% stated they were very or quite satisfied with this decision.	Comment noted. No action required.
	Infliximab is not recommended for the treatment of AS NASS is disappointed that NICE has not recommended making infliximab available to people with AS, especially as a number of biosimilar versions of infliximab have entered the market at a significantly lower cost. We would note that the cost effectiveness analysis was based upon the NHS list price and our understanding is that the tender process has resulted in a significantly lower price. This would alter the cost /benefit ratio. 77% of people in the survey who had an opinion on this issue, felt very or quite dissatisfied with this decision. 525 people commented on the reasons for their response, analysing these responses, the main reason behind this dissatisfaction was that people felt AS is a complex condition and they wanted their clinician to be able to choose the best option for them. As there are so few options currently available for the treatment of AS, people felt their rheumatologist should be able to choose from they currently licensed and available options. It was noted that the different mode of administration could	Comment noted. Adalimumab, certolizumab pegol, etanercept, and golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People

Consultee	Comment [sic]	Response
	make this the best option for some people.	currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop (see FAD section 1.1). The Committee discussed the new ICERs presented by the companies marketing biosimilar versions of infliximab, in response to the appraisal consultation document, using lower prices for their products to reflect the tendering process that was taking place during the consultation period. The Committee noted the updated base-case analyses provided by the Assessment group that included both the highest price the NHS would need to pay for infliximab based on the contract prices and infusion costs based on the national tariff to deliver simple parenteral chemotherapy and agreed that these analyses showed that the cost-effectiveness of infliximab was within the range considered to be a cost-effective use of NHS resources (see FAD section 4.67).
	Treatment with another anti TNF is not recommended for people whose disease has not responded to treatment with the first anti TNF, or those who had an initial response which was then lost NASS is very concerned that NICE has specifically stated that treatment with another anti TNF is **not** recommended for people whose disease has not responded to treatment with the first anti TNF, or those who had an initial response which was then lost. We want to highlight that no restriction has been placed on the switching of anti TNF therapy in the psoriatic arthritis guidelines (TA199). This decision was taken in the absence of any evidence about the switching of anti TNF therapy in psoriatic arthritis. NASS feels this sets a precedent. If TA199 is silent on the issue of switching anti TNF in the absence of evidence, the ankylosing spondylitis guidelines should also be silent on the issue. 92% of people in the survey were very or quite dissatisfied with this decision, with the vast majority of these feeling very dissatisfied. 586 commented on the reasons for their response. Many of the people taking part in the survey started their anti TNF as a last option when NSAIDs either no longer helped with the pain or stiffness or had caused side effects such as stomach bleeds or kidney problems. There was huge concern that if their anti TNF had stopped working effectively and they were not allowed to try a second, there would simply be no other treatments available for them. This is effectively condemning people with severe, active AS to a life without access to treatment.	Comment noted. Treatment with another TNF alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to treatment with the first TNF-alpha inhibitor or had an initial response which was then lost (see FAD section 1.5). Comment noted. The Committee discussed whether it was appropriate to consider treatment with a second or third TNF-alpha inhibitor for a person whose

Consultee	Comment [sic]	Response
	Those currently taking an anti TNF highlighted the beneficial effect it had on their lives, noting that effective treatment meant they were able to continue working and making a positive contribution to society. They also noted that the cost of a 12 week trial of a second anti TNF for a patient would be relatively small compared with the potential benefit. We asked respondents if they were currently taking, or had previously taken, anti TNF therapy. More than half (57%) were currently on anti TNF, one in eleven had previously taken it (9%) and the remainder (34%) had never been on anti TNF. We then asked those currently taking anti TNF therapy, how many anti TNF's, including their current one, they had tried. The majority (74%) have only tried one anti TNF, but a quarter have tried two or more.  The main reasons for trying a different anti TNF were side effects (57%) and loss of efficacy (53%).	disease does not respond to treatment, or for someone who experiences a loss of response, experiences adverse events or becomes intolerant to treatment after 12 weeks of starting treatment. The Committee noted comments that some patients would remain on a sub-optimal treatment if they were unable to switch, at a comparable cost but with decreased QALYs. It also noted the consultation comments that other trials including the ATTRA registry, NOR-DMARD registry, RAPID-axSpA study and RHAPSODY study provided further data, although limited, on the efficacy of subsequent TNF-alpha inhibitor treatment The Committee concluded that although there was limited cost effectiveness evidence for subsequent TNF-alpha inhibitor use, and an exact ICER could not be determined it considered the ICER would be within the range considered to be cost effective use of NHS resources and subsequent TNF-alpha inhibitor treatment could be recommended (see FAD section 4.70).

Consultee	Comment [sic]	Response
	Those who had changed anti TNF were asked about the level of benefit they experienced. As the chart indicates, four in five (79%) felt that switching anti TNF had a moderate to large benefit for them.  Ninety five people commented on how changing anti TNF helped them. It can clearly be seen from this representative selection of comments, what diverse and complex problems people have with both their condition and the anti TNF therapy. This is why NASS believe it is so important to allow rheumatology consultants the flexibility to work with their patients to find the best possible solution for them. *My first anti TNF, etanercept, appeared to make my associated eye conditions (especially uveitis) much worse. Also my AS symptoms continued.* *The first anti TNF coincided with my suffering from continuous bouts of uveitis, which prior to taking it I had never experienced. It was some years later that it was decided that*	Comment noted. The Committee heard from the clinical experts that people who cannot tolerate a first TNF alpha inhibitor or experience adverse effects, are no less likely to respond to an alternative agent. The experts stated that the number of patients is likely to be relatively small at around 6000 people The Committee acknowledged that predicting a disease response in advance was not possible, and that this could have a major impact on a lifelong condition. The Committee concluded that there was a clinical need for subsequent TNF-alpha inhibitor treatments (see FAD section 4.53). Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).

Consultee	Comment [sic]	Response
	I might benefit from a second drug. At this point I was caring for my spouse, who is bed bound with MS, and still working. The benefits of the drug were almost instantaneous and have enabled me to continue working until I have been forced to retire due to my spouses deteriorating health. I am still able to be a full time carer for him, which I am certain would not have been possible had I not been given a second drug. *When I was on my first anti TNF I spent long periods on antibiotics to treat the boils which were a result of the treatment. Since changing I have not experienced the same problem.* *The first anti TNF was by infusion every 8 weeks and the effect wore off after 5-6 weeks. Second anti TNF (Enbrel) was a weekly subcut. self injection at home. The benefit is now continuous.* *I experienced side effects on Humira with little improvement in my pain/stiffness. I felt generally unwell whilst taking it. Simponi was started 70 days after finishing Humira. Now after two doses I am beginning to experience significantly less pain and stiffness and feel generally well for the first time in many years.* *The Humira wore off after a few years. Simponi helps me to access work and support my family rather than being a burden.* *The first anti TNF had no positive effect on my life. I was still in pain, still had morning stiffness, and still couldn't control my life. After changing anti TNF to Enbrel from Humira, I found gradually that my morning stiffness faded somewhat, and I gained more control of the pain, although so much damage had already been done from 12 years of misdiagnosis.* *My first anti TNF gave me some help. The second anti TNF was a massive help and improvement.*	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
The British Society for Rheumatology	The BSR welcomes the appraisal consultation document (ACD) – TNF alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA 233). We agree with the majority of the conclusions, however we are extremely concerned that the ACD does not recommend treatment with another anti-TNF for people whose disease has not responded to treatment with the first anti-TNF, or those who had an initial response which was then lost. We have outlined our response under 4 headings;	

Consultee	Comment [sic]	Response
	1. **Patients in England and Wales may be disadvantaged** At present, Ankylosing Spondylitis (AS) patients in the UK are only allowed access to one anti-TNF, unless they experience an adverse event within 12 weeks of initiating therapy1. The new proposed guidance has not changed this position. In our opinion, this severely limits the therapeutic options for patients, particularly in comparison to Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) where many more biologic treatment options exist. This means that AS patients are placed at a significant disadvantage relative to other patients with inflammatory arthritis. NICE has published a commissioning algorithm for patients with RA which includes guidance on the sequential use of biologics, much of which does not have an evidence base2. No restriction has been placed on switching anti-TNF therapy in the psoriatic arthritis guidelines3. This has set a precedent for other patients with inflammatory arthritis. As TA199 is silent on the issue of switching in the absence of RCT evidence, the axial spondyloarthritis (axSpA) guidelines should also remain silent on this issue. At an International level, The Scottish Medicines Consortium, European League Against Rheumatism and the Assessment of Spondyloarthitis International Society have not advised against or placed any restriction on sequential anti-TNF therapy in axSpA4,5. These documents specifically state “switching to a second TNF blocker might be beneficial especially in patients with loss of response”. This is being interpreted by rheumatologists as an opportunity to switch selected patients to an alternative TNF inhibitor in their respective countries.	Comment noted. Treatment with another TNF alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to treatment with the first TNF-alpha inhibitor or had an initial response which was then lost (see FAD section 1.5).
	2. **Axial SpA is a complex disease requiring an option to switch TNF agents** Axial SpA is a complex disease with a variety of phenotypic manifestations which may evolve and change over time. The biology of inflammatory arthritis and TNF therapies is also complex. We know that TNF inhibitors work via a number of different mechanisms; monoclonal antibodies, receptor blockade etc. For example, if a patient being treated with a TNF inhibitor developed colitis or uveitis, it may be clinically appropriate to change to a different TNF inhibitor. Similarly, in patients who develop human anti-chimeric antibodies (HACAs), it may be clinically appropriate to switch to another agent. Under proposed guidance, if the choice of initial drug proves to be incorrect or inappropriate, patients will not have access to an alternative effective treatment. Clinicians and patients are being placed under unreasonable pressure to select one and one-only TNF inhibitor. 3. **Published data on switching** We accept that there are limited published data on the sequential use of TNF-inhibitors and no RCTs exist, and it is unlikely that these studies will ever be undertaken. On p19 of the ACD, the committee included the DANBIO data in a table6, and stated: “The Assessment Group concluded that, despite a decrease in response rate, sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis”. In addition to the DANBIO data, there are 2 controlled studies (NOR-DMARD, ATTRA)7,8. In NOR-DMARD, 77 of 514 TNF-treated AS patients switched (30 because of inefficacy representing <6% of the total TNF treated population. One-third of these “switch” patients demonstrated a good clinical response. In ATTRA, the response rates of 163 “switch” patients were compared to 1012 patients treated with a first TNF inhibitor. More than 50% of “switch” patients	Comment noted. The Committee discussed whether it was appropriate to consider treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond to treatment, or for someone who experiences a loss of response, experiences adverse events or becomes intolerant to treatment after 12 weeks of starting treatment. The Committee noted comments that some patients would remain on a sub-optimal treatment if they were unable to switch, at a comparable cost but with decreased QALYs. The Committee concluded that although there was limited cost effectiveness evidence for subsequent TNF-alpha inhibitor use, and an exact ICER could not be determined it considered the ICER would be within the range considered to be cost effective use of NHS resources and subsequent TNF-alpha inhibitor treatment could be

Consultee	Comment [sic]	Response
	achieved a major clinical response or partial remission. In both studies, the numbers of patients who needed to switch because of inefficacy was extremely small and there were no difference in outcomes between those switching due to adverse events or inefficacy. Denying this group of patients the opportunity to access sequential therapy would in our opinion place them at a significant clinical disadvantage as there is no alternative effective treatment pathway available. No studies have specifically examined switching in non-radiographic axSpA, however there is no reason to assume that outcomes would be significantly different in this group.	recommended (see FAD section 4.70).
	4. **Implications of a "no switch" policy** If there is no "switch" option patients may remain on sub therapeutic treatment (for example a patient who had an initial excellent response and deteriorates over time yet still by definition meets the response criteria may be better served by an alternative agent. **Conclusion** In our opinion, patients should be allowed to switch to alternative anti-TNF drugs at any point during treatment, whether for reasons of inefficacy or adverse events. We urge the committee to reconsider their position on sequential TNF inhibitors in axial SpA. **References** 1. NICE TA143 2. NICE CG79 3. NICE TA199 4. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. J Braun, J Davis, M Dougados et al. ARD 2006;65(3): 316-20 5. Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of Ankylosing Spondylitis. X Baraliakos; R van den Berg; J Braun; D van der Heijde. Rheumatology. 2012;51(8):1378-1387. 6. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor alpha inhibitor therapy: results from the Danish nationwide DANBIO registry. Glintborg B, Ostergard M, et al. ARD 2013;72(7): 1149-55. 7. Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. E Li, D van der Heijde et al. ARD 2011;70: 157-63 8. Efficacy of the first and subsequent courses of anti-TNF therapy in patients with ankylosing spondylitis – results from the Czech National Register ATTRA. Rheumatologia 2012; 50(4): 294-306	Comment noted. The Committee heard that the inability to switch agents results in many patients remaining on their sub-optimal TNF-alpha inhibitor indefinitely because of the lack of access to an alternative more effective option and concluded that there was a clinical need for subsequent TNF-alpha inhibitor treatments (see FAD section 4.53).

Consultee	Comment [sic]	Response
Royal College of Nurses	The RCN invited members caring for people with ankylosing spondylitis to review the documents on its behalf. **Appraisal Consultation Document – RCN Response** The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: i) Has the relevant evidence been taken into account? The evidence considered seems comprehensive.	Comment noted. No action required.
	ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Our members have asked that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with ankylosing spondylitis. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. No action required.
	iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Our members working in this area of health reviewed the recommendations of the Appraisal Committee and refer to section 4.12 of the ACD, in which the Assessment Group concluded that sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis. Our members are however, concerned that despite this evidence the committee has still not agreed to the sequential use of TNF-alpha inhibitors in the draft recommendations. In this respect, the committee seems to be ignoring the average age of patients with ankylosing spondylitis and the need to keep this group of patients in employment. In view of this, would like to ask the committee to reconsider its decision in the light of the conclusion of the Assessment Group for this group of patients. We would advise that the recommendation should allow treatment with another TNF-alpha inhibitor for people whose disease has not responded to treatment with the first TNF-alpha inhibitor.	Comment noted. Treatment with another TNF-alpha inhibitor is recommended for people who cannot tolerate, experience adverse effects, or whose disease has not responded to treatment with the first TNF-alpha inhibitor or had an initial response which was then lost (see FAD section 1.5).
	Our members also raised a query about the assessment timings. At present patients have to wait three months between assessments before they can have biologics. They are the only patients in the rheumatology group that have to wait that long. Is there any evidence that supports the rationale for this wait and would the committee consider reducing it to a monthly gap as per rheumatology arthritis and psoriatic arthritis patients? It seems odd and unfair that only this group of patients have to wait	Comment noted. The Committee concluded that the decision to continue treatment in clinical practice should be based on the broader definition of response to treatment outlined in British

Consultee	Comment [sic]	Response
	this long between assessments. Other than the point made above, our members consider that the ACD seems to have addressed issues relating to non-radiographic axial spondyloarthritis.	Society of Rheumatology (BSR) guidelines and the previous technology appraisal: a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction of the spinal pain VAS by 2 cm or more. If an adequate response is not achieved 12 weeks after treatment initiation, treatment should be discontinued (see FAD section 4.68).
	iv) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None that we are currently aware of.	Comment noted. No action required.
	v) Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document? We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. No action required.
Royal College of Physicians	Please take this email as confirmation that the RCP wishes to endorse the response of the BSR to the above ACD.	Comment noted. No action required.
AbbVie	We are pleased with the preliminary decision to recommend adalimumab, certolizumab pegol, etanercept and golimumab as treatment options for active ankylosing spondylitis (AS) and adalimumab, certolizumab pegol and etanercept, as treatment options for non-radiographic axial spondyloarthritis (nr-ax SpA). We have some comments which we present under the questions asked by NICE and we propose that our feedback is taken into consideration at the next appraisal meeting. **Section 1. Has all of the relevant evidence been taken into account?** 1.1 Sequential treatment 1.1.1 Removal of the restriction on switching to an alternative anti-tumour necrosis factor in the event of a patient not responding or losing initial response	

Consultee	Comment [sic]	Response
	AbbVie welcomes the acknowledgement in the ACD that there are data showing the benefits of switching to another anti-tumour necrosis factor (anti-TNF) in case of treatment failure. Whilst AbbVie understands that the Committee was unable to recommend switching due to the lack of cost-effectiveness data, AbbVie notes the Committee considered the evidence for sequential treatment is based on registry data alone (underlined text): *4.59. The Committee considered the clinical evidence for treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond to treatment, or for someone who experiences a loss of response (sequential treatment)… However, the Committee was concerned that this evidence was based on registry data alone and was uncertain about the true magnitude of the benefit of sequential treatment in ankylosing spondylitis*	
	AbbVie wishes to point out that in the Assessment Report reference is made to the RHAPSODY study, described in more detail in the AbbVie submission. Briefly, in this large, European, open-label study 326 participants were treated with adalimumab after infliximab or etanercept, or after both these drugs. Response rates at 12 weeks in the anti-TNF experienced participants who discontinued a prior anti-TNF due to loss of response, although lower than in the anti-TNF naïve participants, were still high: BASDAI 50 – 42% and ASAS40 – 43%. Additionally, AbbVie notes that the RAPID-axSPA study with certolizumab pegol, mentioned in the ACD, and discussed in the Assessment Report and the manufacturer's submission, was a randomised, double-blind, placebo controlled trial which included both anti-TNF naïve and experienced patients. It appears from the ACD that this information may not have been considered by the Committee.	Comment noted. Treatment with another TNF-alpha inhibitor is recommended for people who cannot tolerate, experience adverse effects, or whose disease has not responded to treatment with the first TNF-alpha inhibitor or had an initial response which was then lost (see FAD section 1.5).
	AbbVie considers that given the typical age of patients starting anti-TNF therapy and the need for lifelong control of their disease it is very important for NICE to permit switching of anti-TNF therapy in case of treatment failure due to loss of efficacy. We believe this view is supported by patients, as reflected in the near unanimous response of the members of the National Ankylosing Spondylitis Society (NASS) to the question on whether patients should try a second anti-TNF if a first one's effectiveness wears off over time. This is also supported by the ASAS/EULAR recommendations for the management of ankylosing spondylitis[1]. AbbVie is also aware that there are instances where patients are able to access a second anti-TNF, but that this depends on the clinical commissioning group to which the patient belongs i.e. postcode prescribing, which is not in the spirit of ensuring that all patients have access to the same drug. Lastly, whilst the ACD acknowledges that extra-articular manifestations (EAMs) should be considered when choosing an anti-TNF, EAMs may only become apparent during the course of the disease, i.e. after the start of treatment. In such instances a patient would benefit from switching to another anti-TNF if such treatment has greater efficacy for the particular EAM than the first anti-TNF. Based on the points outlined above, AbbVie would request reconsideration on the recommendation not to switch anti-TNF therapy (Section 1.6).	Comment noted. The Committee also noted the consultation comments that other trials including the ATTRA registry, NOR-DMARD registry, RAPID-axSpA study and RHAPSODY study provided further data, although limited, on the efficacy of subsequent TNF-alpha inhibitor treatment The Committee concluded that although there was limited cost effectiveness evidence for subsequent TNF-alpha inhibitor use, and an exact ICER could not be determined it considered the ICER would be within the range considered to be cost effective use of NHS resources and subsequent TNF-alpha inhibitor treatment could be recommended (see FAD section 4.70).

Consultee	Comment [sic]	Response
	Removal of this restriction would bring the guidance for AS and non-radiographic axial SpA in line with NICE recommendations for psoriatic arthritis, psoriasis, Crohn's Disease and ulcerative colitis, none of which contain a recommendation against switching to a different anti-TNF in case of treatment failure. **2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** 2.1 Wording on choice of treatment 2.1.1 Amendment to section 1.4 to clarify choice of treatment The preliminary recommendations state that: 1.4 The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, and may include consideration of associated conditions. If more than 1 treatment is suitable, the least expensive should be chosen AbbVie considers the wording "associated conditions" in the above section may be ambiguous in its current format. If it is meant to refer to extra-articular manifestations as per the discussions in sections 4.50, 4.58 and 4.71 then we request that the wording in section 1.4 be amended to the underlined text below: 1.4 The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, and may include consideration of associated conditions such as *extra-articular manifestations*. If more than 1 treatment is suitable, the least expensive should be chosen This amendment would enable the reader to understand what is meant with the term "associated conditions" without the need to review the whole document.	Comment noted. The choice of treatment should be made on an individual basis after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include consideration of associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable , including the biosimilars of infliximab, the least expensive (taking into account administration costs and patient access schemes) should be chosen (see FAD section 1.3).
	2.2 Yearly cost for infliximab 2.2.1 Amendment to cost of infliximab The ACD states that 3.18 …For a patient with a body weight of 73 kg, the annual cost for first year of treatment with infliximab therapy (including 3 induction doses) is estimated at between £16,785 and £13,428 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks). As stated in our response to the Assessment Group report, AbbVie considers it is important to consider the distribution of patient weight rather than summary statistics for weight alone when the treatment cost for a population is being calculated. Measures other than the mean cost calculated	Comment noted. No action required.

Consultee	Comment [sic]	Response
	based on patient weight distribution do not provide information about the cost of treating all patients. As such, AbbVie requests that the mean cost for infliximab should be amended in ACD to take account of the full distribution in patient weight of AS patients. This will result in a more accurate and reasonable estimation of the annual treatment cost of infliximab. **3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS**? AbbVie has no comments on this point. **4. Are there any aspects of the recommendations that need particular consideration to ensure NICE avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** AbbVie has no comments on this point. REFERENCES 1 Braun J, van den Berg R, Baraliakos X et al. 2010 update of the ASA/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011; 70; 896-904	Comment noted. No action required. Comment noted. No action required.
Hospira	**1.1. Introduction** Adalimumab, etanercept, golimumab and infliximab (Remicade and Inflectra) have marketing authorisations in the UK for the treatment of adults with severe active ankylosing spondylitis that has responded inadequately to conventional therapy. Certolizumab pegol has a marketing authorisation in the UK for the treatment of 'adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs'. It is anticipated that implementing the draft positive recommendations (detailed in the ACD, May 2015) for the ongoing appraisal [ID694] (NICE, 2015), may lead to increased treatment costs due to the increased number of patients with ankylosing spondylitis receiving TNF-alpha inhibitors. The average lifetime treatment costs for adults, taking into account drug costs, administration costs and monitoring costs per 12-week cycle, are presented for conventional therapy and TNF-alpha inhibitors (Table 1). The incremental cost for treatment with proprietary infliximab (Remicade) compared with conventional therapy is £40,267. Costs for treatment with infliximab may change if biosimilars become available as a result of lower drug costs: i. The list price of the biosimilar infliximab Inflectra, is lower than that of the proprietary infliximab (Remicade). ii. There is also potential for additional cost savings associated with Inflectra versus all comparators, due to the provision of Inflectra on NHS tender frameworks at prices lower than	

Consultee	Comment [sic]	Response
	the NHS list price. There are differences in price between tender regions as the prices are based on the current market size for infliximab. The lowest Inflectra in-market tender price of (£[redacted]) is at [redacted] % discount off the proprietary infliximab (Remicade) list price; the highest Inflectra in-market price (£[redacted]) is at [redacted]% discount off the proprietary infliximab (Remicade) list price. The NHS tendering process is complete and the in-market prices are nationally available within the range of [redacted]% and [redacted]% discount off the proprietary infliximab (Remicade) list price. Each NHS tender region applies different timeframes to the tender frameworks. In this case the shortest framework is 10 months and the longest 24 months. The Commercial Medicines Unit issues re tender information towards the end of each framework period. Differences in cost between Inflectra and proprietary infliximab (Remicade) are due to drug costs alone, not due to dosing, as the treatment schedule is the same for both drugs, as stated below: ● 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. ● If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given. This document presents the results of cost-effectiveness analyses conducted using both the list and tender prices of Inflectra within the Assessment Group's model, in order to provide a representation of the actual cost to the NHS of using Inflectra in clinical practice for the treatment of severe active ankylosing spondylitis.	Comment noted. The Committee noted that the companies' representatives present at the meeting were able to confirm that the tendering process was complete and that the Commercial Medicines Unit contract prices were now available in the NHS. The Committee noted the updated base-case analyses provided by the Assessment group that included both the highest price the NHS would need to pay for infliximab based on the contract prices and infusion costs based on the national tariff to deliver simple parenteral chemotherapy and agreed that these analyses showed that the cost-effectiveness of infliximab was within the range considered to be a cost-effective use of NHS resources (see FAD section 4.67).
	1.2. Economic considerations Cost-effectiveness analyses conducted using the assessment group model indicated that among TNF-alpha inhibitors, proprietary infliximab (Remicade) has the highest treatment costs resulting in the highest incremental cost effectiveness ratio (ICER) compared with conventional therapy. In Table 1, the cost shown for Inflectra is the NHS list price, which is lower than the list price for proprietary infliximab (Remicade). Cost-effectiveness analyses conducted using a price for Inflectra that incorporates a 40% discount to the list price of proprietary infliximab results in treatment costs that are comparable to the other TNF-alpha inhibitors. The resulting ICER for Inflectra is comparable to that of the other TNF-alpha inhibitors, and is lower than the ICER for proprietary infliximab (Table 2). These outcomes are also obtained when the price used for Inflectra is the lowest tendered price (Table 3), the highest tendered price (Table 4), or the average tendered price in the UK (Table 5). Table 1: Inflectra List Price	Comment noted. The Committee noted section 5.5.2 of the NICE 'Guide to the methods of technology appraisal' (2013) which states: "When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS." The Committee therefore concluded that infliximab could also be recommended as an option for treating adults with ankylosing spondylitis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs only if the infliximab product with the lowest acquisition cost is

Treatment	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
Conventional Therapy	7.231		106,486		
Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
Golimumab	7.835	0.605	128,669	22,183	36,681

Consultee	Comment [sic]	Response

Adalimumab	7.835	0.605	128,754	22,267	36,821
Etanercept	7.835	0.605	129,132	22,645	37,447
Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
Infliximab – biosimilar (Inflectra)	7.835	0.605	[redacted]	[redacted]	[redacted]
Infliximab – proprietary (Remicade)	7.835	0.605	146,754	40,267	66,586

Note: All costs shown are based on the dose for an adult of 73 kg. QALY, Quality-adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio, PAS, patient access scheme

Table 2: Inflectra at 40% discount to Remicade price

Treatment	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
Conventional Therapy	7.231		106,486		
Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
Golimumab	7.835	0.605	128,669	22,183	36,681
Adalimumab	7.835	0.605	128,754	22,267	36,821
Etanercept	7.835	0.605	129,132	22,645	37,447
Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
Infliximab – biosimilar (Inflectra)	7.835	0.605	[redacted]	[redacted]	[redacted]
Infliximab – proprietary (Remicade)	7.835	0.605	146,754	40,267	66,586

Note: All costs shown are based on the dose for an adult of 73 kg. QALY, Quality-adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio, PAS, patient access scheme

Table 3: Inflectra at lowest tendered price

Treatment	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
Conventional Therapy	7.231		106,486		
Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
Infliximab – biosimilar (Inflectra)	7.835	0.605	[redacted]	[redacted]	[redacted]
Golimumab	7.835	0.605	128,669	22,183	36,681
Adalimumab	7.835	0.605	128,754	22,267	36,821

used. People already receiving infliximab should be able to continue on their existing product (see FAD section 4.67).

Comment noted. See above.

Comment noted. See above.

Consultee	Comment [sic]	Response

Etanercept	7.835	0.605	129,132	22,645	37,447
Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
Infliximab – proprietary (Remicade)	7.835	0.605	146,754	40,267	66,586

Note: All costs shown are based on the dose for an adult of 73 kg. QALY, Quality-adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio, PAS, patient access scheme

Table 4: Inflectra at highest tendered price

Treatment	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
Conventional Therapy	7.231		106,486		
Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
Golimumab	7.835	0.605	128,669	22,183	36,681
Adalimumab	7.835	0.605	128,754	22,267	36,821
Etanercept	7.835	0.605	129,132	22,645	37,447
Infliximab – biosimilar (Inflectra)	7.835	0.605	[redacted]	[redacted]	[redacted]
Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
Infliximab – proprietary (Remicade)	7.835	0.605	146,754	40,267	66,586

Note: All costs shown are based on the dose for an adult of 73 kg. QALY, Quality-adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio, PAS, patient access scheme

Table 5: Inflectra at average tendered price

Treatment	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
Conventional Therapy	7.231		106,486		
Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
Golimumab	7.835	0.605	128,669	22,183	36,681
Adalimumab	7.835	0.605	128,754	22,267	36,821
Etanercept	7.835	0.605	129,132	22,645	37,447
Infliximab – biosimilar (Inflectra)	7.835	0.605	[redacted]	[redacted]	[redacted]
Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809

Comment noted. See above.

Comment noted. See above.

Consultee	Comment [sic]	Response
		Comment noted. Adalimumab, certolizumab pegol, etanercept, and golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop (see FAD section 1.1).
Merck Sharpe and Dohme	Our key concern is that the Appraisal Committee has decided not to permit 'switching' between TNF-α inhibitors except when intolerance to the first agent occurs in the first 3 months of treatment before the assessment of response. As TNF-α inhibitors are the only class of therapies available for AS and	Comment noted. Treatment with another TNF-alpha inhibitor is recommended for people who cannot tolerate, experience

Infliximab – proprietary (Remicade)	7.835	0.605	146,754	40,267	66,586	

Note: All costs shown are based on the dose for an adult of 73 kg. QALY, Quality-adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio, PAS, patient access scheme

1.3 Conclusions

At the NHS list price for Inflectra, treatment costs remain lower than for proprietary infliximab (Remicade) (Table 1).

We suggest that the Assessment Group consider Inflectra in-market tender prices in the appraisal as they represent the actual cost to the NHS in clinical practice. This approach was taken in the NICE technology appraisal of erythropoiesis-stimulating agents (ESAs) [TA323]; (NICE, 2014). In a scenario analysis, the Assessment Group applied the best contract prices available for the ESAs to its base-case analysis, rather than the prices listed on the British National Formulary. The Committee concluded that the contract prices of the ESAs were the most relevant prices as they reflected the actual prices paid by the NHS for ESAs based on a 'price-volume' agreement with the companies (NICE, 2014).

Using the conservative approach of the lowest discounted tender price available across the UK, Inflectra is cost saving versus proprietary infliximab (Remicade) (Table 4). Using the highest discounted tender price, Inflectra represents even greater value for money to the NHS; Inflectra is associated with a lower ICER compared to conventional therapy than for golimumab, adalimumab, etanercept, certolizumab pegol and proprietary infliximab (Remicade) (Table 3). Using the average discounted tender price for Inflectra results in an ICER that is lower than for proprietary infliximab (Remicade) and comparable to the other TNF-□ inhibitors (Table 5).

For the treatment of severe active ankylosing spondylitis, the use of Inflectra compared with proprietary infliximab (Remicade) provides cost savings to the NHS.

References

National Institute for Health and Care Excellence (NICE); 2015. Appraisal consultation document: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233), May 2015.

National Institute for Health and Care Excellence (NICE); 2014. Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142). NICE technology appraisal guidance [TA323], November 2014.

Consultee	Comment [sic]	Response
	nr-ax SpA this decision effectively condemns patients who fail to respond or who lose response to one TNF-α inhibitor to returning to conventional treatment alone (which was not effective in managing their condition). This situation is acknowledged to lead to considerable patient anxiety (Section 4.24) and could disproportionately affect younger patients for the reason that longer disease duration may require more options for treatment. We disagree with the Appraisal Committee's position on 'switching' for a number of reasons:	adverse effects, or whose disease has not responded to treatment with the first TNF-alpha inhibitor or had an initial response which was then lost (see FAD section 1.5).
	1. Second-line and third-line TNF-α inhibitors have been demonstrated to be efficacious in real-world patients Data from the DANBIO registry (summarised in Section 4.11 of the ACD) demonstrate that sequential treatment with TNF-α inhibitors is efficacious, with small reductions in absolute efficacy with each subsequent line of therapy. The Assessment Group, patient experts, clinical experts, and the Appraisal Committee all acknowledge this finding (Sections 4.12, 4.24, and 4.59). Therefore, it is surprising that the Appraisal Committee feels unable to permit 'switching' in the preliminary recommendation. One of the reasons given in the ACD relates to the lack of data from randomised clinical trials (RCTs). The NICE Methods Guide does permit the use of non-randomised studies where there is a need to supplement RCT data, with appropriate recognition of the limitations. One such limitation raised by the Assessment Group is that "registries are unreliable because of their selection bias"; however, this is arguably also true for RCTs where enrolled patients are generally fitter than the general population of patients with that condition. In this case we believe it to be beneficial to have data from a real-world population of patients in whom the treatments will be used, as an indicator of likely treatment effects. The existence of patients who have had multiple TNF-α inhibitors within the database also highlights the real clinical need for multiple treatment options in clinical practice.	Comment noted. The Committee also noted the consultation comments that other trials including the ATTRA registry, NOR-DMARD registry, RAPID-axSpA study and RHAPSODY study provided further data, although limited, on the efficacy of subsequent TNF-alpha inhibitor treatment The Committee concluded that although there was limited cost effectiveness evidence for subsequent TNF-alpha inhibitor use, and an exact ICER could not be determined it considered the ICER would be within the range considered to be cost effective use of NHS resources and subsequent TNF-alpha inhibitor treatment could be recommended (see FAD section 4.70).
	The cost-effectiveness analysis conducted by one of the manufacturers indicated that ICERs for second-line TNF-α inhibitors are ~£1000 higher than for TNF-α inhibitors used first-line. This should reassure the Appraisal Committee that TNF-α inhibitors used in this way are likely to remain a cost-effective use of NHS resources. We acknowledge that the Assessment Group found there to be some limitations with the sequential modelling; however, we would like to see improvements made to this work and further exploration, rather than it being judged as insufficient to support decision-making.	Comment noted. The Committee noted that one company had explored a population containing both people receiving their first TNF-alpha inhibitor and a small number switching to a subsequent TNF-alpha inhibitor. Taking into account the small number of patients switching (approximately 6%in their model) and the reduced efficacy of subsequent TNF alpha inhibitors in previous treatment failures, there was only an estimated £1000 increase in the ICER per QALY gained in the population containing both first line and switch patients compared with first line use alone

Consultee	Comment [sic]	Response
		(see FAD section 4.69).
	2. Limiting patients with AS/nr-ax SpA to one opportunity for biologic treatment is misaligned with other diseases in which biologics are used In cases of inadequate response to first-line biologic therapy patients with rheumatoid arthritis are able to receive treatment with alternative biologics i.e. rituximab and tocilizumab. Patients with psoriatic arthritis are permitted to receive ustekinumab after "the person has had treatment with 1 or more TNF-alpha inhibitors" (TAG 340). Finally, the switching of biologics is permitted in the management of psoriasis. Given this context, it is not clear whether it is equitable to deny patients with AS and nr-ax SpA the opportunity to find the right biologic therapy from those available to manage their condition.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
	We note that infliximab has not received a recommendation for AS, and we reiterate our previous comments (submitted in response to the Assessment Group report) around the 'class effect' assumption; we believe that this underestimates the efficacy of Remicade, leading to the judgment that this medicine is not a cost-effective use of NHS resources. Ultimately we believe that patients and clinicians would benefit from access to all efficacious medicines, as part of their armamentarium with which to manage the condition. Finally, we wish to highlight a statement in the ACD that needs to be amended. In Section 3.3 it states: "Golimumab and infliximab do not currently have a marketing authorisation in the UK for non-radiographic axial spondyloarthritis". Simponi has now received a positive CHMP opinion for nr-ax SpA. Consequently, this statement will be incorrect when final guidance is issued (and potentially when the Final Appraisal Determination is issued, contingent on timelines for EMA approval).	Comment noted. Adalimumab, certolizumab pegol, etanercept, and golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop (see FAD section 1.1).
Napp	Napp Pharmaceuticals Limited are disappointed to read that The Committee has recommended that NICE should exclude infliximab from the list of approved TNF-alpha inhibitors in its guidance for the treatment of ankylosing spondylitis (AS). We were present at the committee meeting on February 25th and believe that patient representatives made a strong case to include intravenous infliximab as an alternative for those patients not wishing to use or who are unable to use sub-cutaneous medicines. In section 4.25 of the ACD the patient groups went on to suggest a group of people who might benefit from an infusion and in fairness, disadvantages were also discussed. It is clear from The Committee papers and the consultation document that infliximab offers people	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).

Consultee	Comment [sic]	Response
	with AS an option which in clinical trials has demonstrated a rapid and yet sustained reduction in symptoms as measured by BASDAI and BASFI scores similar to other anti-TNFs. In fact in section 4.8 "the Assessment Group (AG) noted that the results for infliximab at 10-16 weeks appeared slightly better than results for the other TNF-alpha inhibitors (although the credible intervals are wide)." In section 4.9 "the AG concluded that the long-term benefit of TNF-alpha inhibitors appear similar across treatments". Although patients see a value in having an alternative delivery route to the other 4 interventions The Committee concluded (Section 4.71) it could not recommend the use of infliximab simply on the basis of another treatment choice. This would suggest that infliximab is not being excluded due to clinical reasons but primarily on grounds of cost-effectiveness. The Committee noted that the ICERs for infliximab were higher than the other TNF-alpha inhibitors and concluded that the ICERs for infliximab were not within the range considered to be a cost-effective use of NHS resources. The Committee suggested that this was largely due to the higher administration costs. We can demonstrate that there is no one infusion cost that can be quoted reliably and the variation is such that the Assessment Group for the recent RA MTA applied a different cost for infusions to that used in this appraisal in fact it was nearly half of that used here: £154 vs £291. Furthermore by using the list price rather than the true (i.e. local procurement tender) NHS acquisition price for the biosimilar infliximab the guidance is biased against the biosimilar versions of infliximab. We suggest that there are two parts to this problem: • the first is that NICE does not seem to have a mechanism within the methodology for dealing with tender prices as the agreements are not national and may not be concluded at the time of appraisal • and the second is how to differentiate the lower cost and therefore more cost-effective Remsima® biosimilar infliximab from the originator in the NICE guidance. This is obviously an unforeseen problem that has arisen since NICE published its position paper on biosimilars. http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/biosimilars-statement.pdf. Point (*e)* in the position statement says that *"The Department of Health in England has confirmed that a technology remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market".* Unfortunately this has not taken into account the potential effect of the significantly lower price and how this affects the ICER leading to the need to differentiate the more cost-effective biosimilar. When calculating the cost effectiveness of infliximab the AG has used the NHS list prices for infliximab whether for the originator or biosimilar versions. (£419.62 for 100mg Remicade®, MSD and £377.66 for Remsima, Napp Pharmaceuticals Limited). This results in ICERs that do not reflect the true cost to the NHS as infliximab is subject to the tendering process.	Comment noted. The Committee noted comments received in response to the appraisal consultation document regarding the infusion cost of infliximab. The Committee discussed the infusion cost, stating that the infusion cost of infliximab was too high in the Assessment Group's model and that a recent NICE consultation document for rheumatoid arthritis had used the price of £154 for infliximab infusion. The Committee noted that a range of sources had been used in other appraisals including inpatient and outpatient day costs. The clinical experts stated that infusion costs in their respective hospital trusts ranged between £140 and £168. The Committee was aware that the national tariff to deliver simple parenteral chemotherapy was £159, and the clinical experts agreed that this cost was reasonable. The Committee concluded that the cost of infliximab infusion was likely to be in line with the national tariff and lower than that used in the Assessment Group's model (see FAD section 4.65).

Consultee	Comment [sic]	Response
	The AG were able to demonstrate that by using the lower published NHS acquisition price the ICER for biosimilar infliximab, Remsima, is lower than that of the originator Remicade. However as the real acquisition price is subject to the tendering process it has not been possible for the AG to look at the effect that tender pricing has on the ICER. **AG ICERs** / **Rebound to Baseline** / **Rebound to Natural history** **Infliximab** £ 40,576 / £ 66,529 **Remsima** £ 36,751 / £ 60,222 We have applied a range of lower tender prices and varying infusion costs to the executable model in order to test its accuracy. We present our findings in the tables below. We show for comparison Tables 8 and 9 from the ACD. We are unable to calculate the Rebound to Baseline ICERs as we do not have a model for this; however we would suggest that the ICERs for Remsima would be similar to the other TNF-alpha inhibitors. **Table 8. Base case results for ankylosing spondylitis: rebound to baseline** Conventional therapy: Costs (£) 110,821; QALYs 7.245; Incremental costs (£) -; Incremental QALYs -; ICER (£/QALY) - Golimumab: 130,173; 8.163; 19,352; 0.918; 21,079 Adalimumab: 130,257; 8.163; 19,436; 0.918; 21,170 Etanercept: 130,630; 8.163; 19,810; 0.918; 21,577 Certolizumab: 132,059; 8.163; 21,238; 0.918; 23,133 Infliximab: 148,073; 8.163; 37,252; 0.918; 40,576 ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year The ICER for Remsima biosimilar infliximab at list price is calculated by the AG to be £36,751	Comment noted. The Committee noted that the companies' representatives present at the meeting were able to confirm that the tendering process was complete and that the Commercial Medicines Unit contract prices were now available in the NHS. The Committee noted the updated base-case analyses provided by the Assessment group that included both the highest price the NHS would need to pay for infliximab based on the contract prices and infusion costs based on the national tariff to deliver simple parenteral chemotherapy and agreed that these analyses showed that the cost-effectiveness of infliximab was within the range considered to be a cost-effective use of NHS resources (see FAD section 4.68). Comment noted. The Committee noted section 5.5.2 of the NICE 'Guide to the methods of technology appraisal' (2013) which states: "When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the

Consultee	Comment [sic]	Response
	Table 9. Base case results for ankylosing spondylitis: rebound to natural history Conventional therapy: Costs (£) 109,933; QALYs 7.265; Incremental costs (£) -; Incremental QALYs -; ICER (£/QALY) - Golimumab: Costs (£) 131,960; QALYs 7.867; Incremental costs (£) 22,027; Incremental QALYs 0.603; ICER (£/QALY) 36,554 Adalimumab: Costs (£) 132,045; QALYs 7.867; Incremental costs (£) 22,111; Incremental QALYs 0.603; ICER (£/QALY) 36,695 Etanercept: Costs (£) 132,423; QALYs 7.867; Incremental costs (£) 22,489; Incremental QALYs 0.603; ICER (£/QALY) 37,322 Certolizumab: Costs (£) 133,851; QALYs 7.867; Incremental costs (£) 23,918; Incremental QALYs 0.603; ICER (£/QALY) 39,693 Infliximab: Costs (£) 150,022; QALYs 7.867; Incremental costs (£) 40,088; Incremental QALYs 0.603; ICER (£/QALY) 66,529 ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year The ICER for Remsima biosimilar infliximab at list price is calculated by the AG to be £60,222 From the executable model we tested the assumption that the ICER was sensitive to infusion cost and to the cost of infliximab. We noted that the AG used a body weight of 73kg for its calculations. We also note that in the executable model it was assumed that all patients using injectable TNF-alpha inhibitors were able to give the treatment themselves and no nursing or follow up home or GP appointments were assumed. Using the executable model for Rebound to Natural History we have produced deterministic ICERs for Remsima compared to conventional therapy for 3 different infusion costs (£1871, £2912 and £3141. The ICERs range from best case £31,272 to the worst case (highest cost and highest infusion cost) £61,371. (Please see Table 1 A to C). Note that there appears to be considerable variability in the published infusion costs from as low as £107 to £3141.	reference-case analysis to best reflect the price relevant to the NHS." The Committee therefore concluded that infliximab could also be recommended as an option for treating adults with ankylosing spondylitis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs only if the infliximab product with the lowest acquisition cost is used. People already receiving infliximab should be able to continue on their existing product (see FAD section 4.67). Comment noted. See above

Consultee	Comment [sic]	Response
	Table 1 Scenario A **Infusion cost £291 as per AG**	Comment noted. See above

Remsima Price (£)	Strategy	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
	Conventional Therapy	7.231		106,486		
	Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Golimumab	7.835	0.605	128,669	22,183	36,681
	Adalimumab	7.835	0.605	128,754	22,267	36,821
	Etanercept	7.835	0.605	129,132	22,645	37,447
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
377.66	Remsima	7.835	0.605	143,100	36,614	60,545
	Infliximab	7.835	0.605	146,747	40,261	66,576

Consultee	Comment [sic]	Response
	Scenario B **Infusion cost as per 2013 tariff** **other** **£187**	Comment noted. See above.

Remsima Price (£)	Strategy	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
	Conventional Therapy	7.231		106,486		
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Golimumab	7.835	0.605	128,669	22,183	36,681
	Adalimumab	7.835	0.605	128,754	22,267	36,821
	Etanercept	7.835	0.605	129,132	22,645	37,447
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
377.66	Remsima	7.835	0.605	140,840	34,354	56,808
	Infliximab	7.835	0.605	144,487	38,001	62,839

Consultee	Comment [sic]	Response

Scenario C **Infusion cost as per 2013 tariff** **o/patients** **£314**

Remsima Price (£)	Strategy	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
	Conventional Therapy	7.231		106,486		
	Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Golimumab	7.835	0.605	128,669	22,183	36,681
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Adalimumab	7.835	0.605	128,754	22,267	36,821
	Etanercept	7.835	0.605	129,132	22,645	37,447
	Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
377.66	Remsima	7.835	0.605	143,600	37,113	61,371
	Infliximab	7.835	0.605	147,247	40,761	67,402

Response: Commented noted. See above.

Published NHS list price in blue

In scenario A using the infusion cost of £291.00 from the AG's model Remsima (priced at example tender prices of [redacted] is more cost-effective than certolizumab without a PAS (ICER 39,321 vs 39,809) and is within the range of all of the other TNF-alpha inhibitors (£33,900 to £39,809) except for the originator infliximab (Remicade) which has an ICER of £66,576.

In scenario B where there is a lower infusion cost of £187.00 (based on the chemotherapy infusion cost) the range of ICERs for the tender price range of [redacted] falls to £31,272 to £35,584. In fact at the lowest two (post tender) prices Remsima is the most cost-effective of all the TNF-alpha inhibitors. In this scenario Remsima falls below or well within the range of ICERs for the other TNF-alpha inhibitors (£33,900 to £39809) except for the originator infliximab (Remicade) which has an ICER of £62,839.

In scenario C we have used the highest cost infusion of £314.00. The ICERs for the other TNF-alpha inhibitors range from £33,900 to £39,809. At the tender price range of [redacted] the ICERS for Remsima range from £35,836 to £40,148. This would yet again make Remsima an equally cost-effective alternative for treating AS. However the originator infliximab (Remicade) has an ICER of £67,402.

Response: Comment noted. See above.

We understand how, when using NHS list prices it has been possible for the committee to give a

Consultee	Comment [sic]	Response
	recommendation on the use of infliximab however this would remove patient access to this valuable biologic medicine. We recommend strongly that the committee re-examine this decision taking into account the discounted tender prices and how given the greater cost-effectiveness of Remsima it is possible to make this valuable biologic medicine more available to people with AS. We have summarised the ICERS for the different Remsima tender price ranges (Table 2) and included the infusion cost ranges. The resultant ICERs are comparable to the other TNF-alpha inhibitors and are similar to those calculated by the AG in Table 9. **Table 2 Summary ICERs Rebound to natural history** **Remsima** | £187 to £314 | [redacted] | **£ 31,272** | **£ 40,148** | ****** **Remsima (AG infusion cost)** | £291 | [redacted] | £ 39,321 | | ****** Certolizumab Pegol PAS | | - | £ 33,900 | | ****** Golimumab | | - | £ 36,681 | | £ 36,554 Adalimumab | | - | £ 36,821 | | £ 36,695 Etanercept | | - | £ 37,447 | | £ 37,322 Certolizumab Pegol | | - | £ 39,809 | | £ 39,693 **Remsima** | £187 to £314 | [redacted] | £ 38,459 | £ 50,209 | ****** **Remsima** | £187 to £314 | £377.66*** | £ 56,808 | £ 61,371 | £ 60,222 Infliximab (Remicade) | £187 to £314 | £419.62 | £ 62,839 | £ 67,402 | £ 66,529 * Base-case ICERS Rebound to Natural History Table 9 ACD ** ICER Not calculated by AG *** NHS List Price Recently the ACD for RA MTA has been circulated for consultation. In the section on Cost of Interventions (4.2.43) it states that; *"In the absence of robust data the Assessment Group used an infusion cost of £154 and a time of 1 hour from the NICE technology appraisal guidance on tocilizumab"* If we were to apply this infusion cost to the AS MTA model it would again support the use of Remsima as it has the effect of lowering the ICERs for Remsima even further as in Table 3 below. **Table 3 Summary ICERs Rebound to natural history applying RA infusion cost of £154**	Comment noted. See above.

Consultee	Comment [sic]	Response

	Infusion cost	Cost per 100mg	ICER Range		ICERS AG Table 9*
Remsima	£ 154	[redacted]	£ 30,087	£ 37,273	**
Certolizumab Pegol PAS			£ 33,900		**
Golimumab			£ 36,681		£ 36,554
Adalimumab			£ 36,821		£ 36,695
Etanercept			£ 37,447		£ 37,322
Certolizumab Pegol			£ 39,809		£ 39,693
Remsima	£ 154	[redacted]	£ 44,460		**
Remsima NHS list price	£ 154	£ 377.66***	£ 55,622		£60,222
Infliximab (Remicade)	£ 154	£ 419.62	£ 61,653		£66,529

* Base-case ICERS Rebound to Natural History Table 9 ACD ** ICER Not calculated by AG

*** NHS List Price

We believe that this clearly demonstrates the difficulty of evaluating the cost-effectiveness of infliximab. By ruling infliximab out of the options available to clinicians the NHS will lose the opportunity to use biosimilar infliximab instead of the originator brand. Furthermore this limits patients' choice to only subcutaneous injectable TNF-alpha inhibitors.

It has been suggested to us by health economists from academic units used for technology appraisals that a way forward would be for Napp to offer a confidential Patient Access Scheme (PAS). We have explored this, and believe that unlike new chemical entities (NCEs) where a discount through a PAS is used to effectively lower the ICER to an acceptable level, it would not be possible to have a PAS and the tender process running simultaneously as this would only lead to confusion for payers.

We know from previous examples that prices reduce over time and this would make the biosimilars even more cost-effective. The biosimilar market is somewhat similar to a generic market where there is more competition and prices are subject to fluctuation.

We are aware that NICE currently is unable to include a national tender price as there are a number of tenders across NHS England. We have demonstrated above that Remsima is cost-effective when compared to conventional therapy.

More biosimilar medicines will soon be available and it is likely that they will be subject to the tender process. NICE may wish to consider how it can handle the discrepancy between the actual price paid by the NHS and NHS list price so that the real actual acquisition price can be included to avoid any confusion in its guidance.

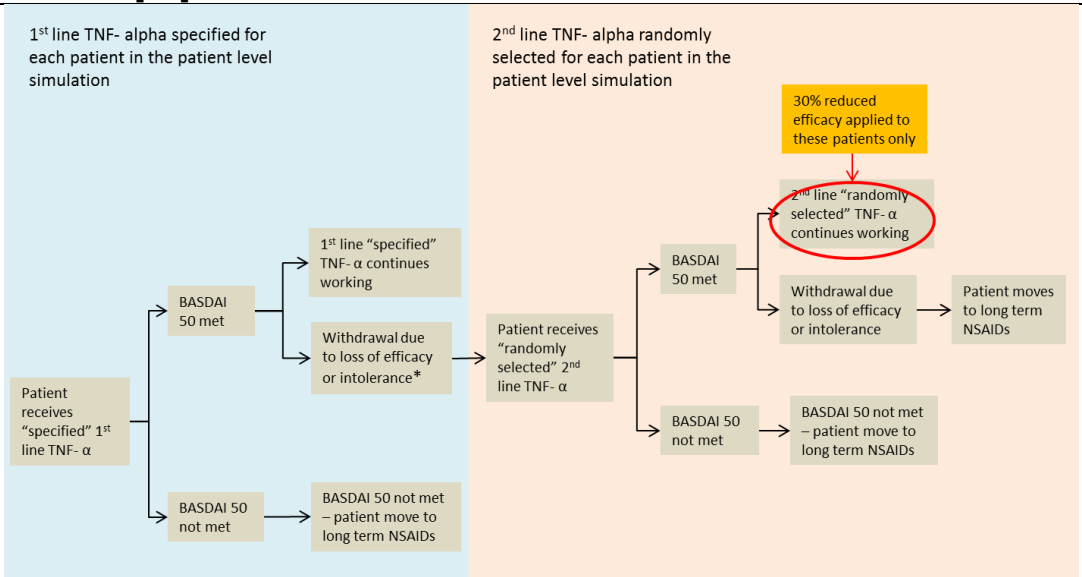
Would it be possible for NICE to consider how it could issue guidance such that CCG's and NHS Trusts could be advised to use infliximab provided it is acquired below a set price £x per 100mg vial?

Comment noted. Adalimumab, certolizumab pegol, etanercept, and golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs.

Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop (see FAD section 1.1).

Consultee	Comment [sic]	Response
	An alternative would be to state that *infliximab is recommended but only at or below the prices agreed within the regional procurement prices*. We estimate that there are approximately 485 patients with AS who would be eligible for infliximab. In summary we urge NICE to reconsider how it calculates the ICERs for medicines that are subject to the tendering process. The current process by only considering published NHS list price is clearly biased against the biosimilars. On this occasion the draft advice is denying patients access to a much lower cost product which we have demonstrated to be cost-effective within the range that is acceptable for the comparator products. We hope that The Committee will be able to review its decision based on the cost-effectiveness of Remsima (biosimilar infliximab) as demonstrated here and allow infliximab as an alternative treatment for AS patients. 1 National Schedule of Reference Costs - Year 2013-14 - NHS trusts and NHS foundation trusts – CHEMOTHERAPY 2 AG executable model referenced to TA143	
Pfizer	Pfizer would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We welcome the interim recommendations and are pleased that the Committee has concluded that etanercept is considered a cost effective use of NHS resources in both indications. Pfizer agree with the Committee's conclusions regarding the validity of key assumptions used in the Assessment Group's economic analysis: • That it is more clinically plausible that patients who stop treatment with TNF-alpha inhibitors have a BASFI that rebounds to baseline score rather than to a poorer state of health than they were at baseline (Section 4.63, page 51). • That there is no evidence to support the implications of the Assessment Group's evidence synthesis used in the base case economic model, ie that patients with more severe disease will be less likely to experience a clinically meaningful benefit than patients with less severe disease (Section 4.61, page 50). Pfizer believe that the combination of the assumptions of a return to baseline and the use of the trial subgroup analyses submitted by the manufacturers (scenario 2) provide the clinically most plausible ICERs from the Assessment Group's economic analysis. We summarise below several points of factual accuracy relating to the interpretation of the analysis on sequential use of TNF-alpha inhibitors. We believe that this analysis submitted by Pfizer (where all patients that withdraw from treatment, whether due to intolerance or loss of efficacy, are entitled to a second line TNF-alpha inhibitor) may have been misinterpreted in the ACD. Section 4.69 (page 55) summarises that the Assessment Group did not consider the analysis as valid as there is only a £1,000 increase in the ICER for sequential treatment when there is a 30% reduction in efficacy for second line treatment. The implication of this is that the Assessment Group would expect a 30%	

Consultee	Comment [sic]	Response
	increase in the ICER (which would be greater than £1,000). In order to ensure that the ACD is factually accurate, Pfizer would like to provide some clarification on how the analysis was performed. 1. In Pfizer's sequential treatment sensitivity analysis, the second line treatment is selected at random from a range of licensed TNF-alpha inhibitors that excludes the specified first-line treatment. This means that the model compares sequential treatment pathways and not specified, second line treatments. Consequently the relationship between second line efficacy and the cost effectiveness of a sequential pathway compared to a standard treatment pathway is non-linear. In our base case analysis patients only receive second line treatment if they achieve a BASDAI 50 response at 12 weeks with first line treatment, but discontinue due to intolerance. The sequential treatment sensitivity analysis also allows those patients who discontinue due to loss of efficacy to commence a second line TNF-alpha inhibitor (see Figure 1 below). The probability of a patient both achieving a BASDAI 50 response at 12 weeks and subsequently discontinuing due to loss of efficacy is relatively low and hence few additional patients receive second line TNF-alpha inhibitor treatment in the sensitivity analysis, limiting the impact upon the ICER. 2. The ACD states in Section 4.32 (page 32): "The ICER for infliximab as a second treatment was £35,840 per QALY (lower than the ICER for infliximab as a first treatment)." This interpretation is incorrect; as explained in point 1, infliximab is not expressly analysed as a second line treatment. The sequential treatment infliximab sensitivity analysis has a lower ICER than the base case because more patients go on to receive the second line TNF-alpha inhibitor, which provides benefit at lower cost than infliximab (which is the highest cost TNF-alpha inhibitor) thus making the whole pathway more cost effective. Pfizer suggest that the ACD is updated to reflect the correct interpretation as follows: the ICER for infliximab as part of a treatment sequence that allows second line treatment after discontinuation due to intolerance or loss of efficacy was £35,840 per QALY (lower than the ICER for infliximab as part of a treatment sequence where second line treatment is only allowed with discontinuation due to adverse events). As a consequence of the points raised in 1.1 and 1.2, Pfizer also suggests deletion of the sentence in section 4.69 (page 55): "The Committee noted that the Assessment Group did not consider this analysis valid." In conclusion, Pfizer welcomes the interim decision of the Appraisal Committee and believe this represents a step forward in the clinical management of patients across the spectrum of axial spondyloarthritis. **Figure 1.**Flow of patients through the Pfizer patient level simulation model in the sequential use sensitivity analysis demonstrating the non-linear relationship between efficacy and outcome.	Commented noted. The Committee noted that one company had explored a population containing both people receiving their first TNF-alpha inhibitor and a small number switching to a subsequent TNF-alpha inhibitor. Taking into account the small number of patients switching (approximately 6%in their model) and the reduced efficacy of subsequent TNF alpha inhibitors in previous treatment failures, there was only an estimated £1000 increase in the ICER per QALY gained in the population containing both first line and switch patients compared with first line use alone (see FAD section 4.70).

Consultee	Comment [sic]	Response
	 *In the base case, patients may only progress to second line TNF-alpha if they withdraw due to intolerance, the diagram presented here is the sensitivity analysis where patients receive second line TNF-alpha therapy whether they withdraw due to intolerance or loss of efficacy	
UCB	UCB welcomes the opportunity to respond to the appraisal consultation document (ACD) from the first Committee meeting for the multiple technology appraisal (MTA) on the use of anti-TNFs in ankylosing spondylitis (AS) and axial spondyloarthritis without the radiographic evidence of AS (nr-axSpA). Following a review of the report we would like to provide a number of comments and observations for consideration by the NICE committee. These comments are structured into two key sections: (1) Comments related to certolizumab pegol, such as details of the approved Patient Access Scheme (PAS) and clarification of the RAPID-axSpA study design, particularly how inclusion of comparable numbers of patients with AS and nr-axSpA was per study protocol and unique feature of this study, allowing direct comparisons of baseline patient burden and treatment response across the spectrum of axial spondyloarthritis (axSpA); (2) General responses to the ACD report, including the patient need for sequential use of anti-TNFs in axSpA and the importance of extra-articular manifestations for patients living with axSpA. **1 Comments related to certolizumab pegol** **1.1 Certolizumab pegol PAS** We welcome the ACD 1 preliminary recommendation for certolizumab pegol without the PAS. UCB	Comment noted. Adalimumab, certolizumab pegol, etanercept, and golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (see

Consultee	Comment [sic]	Response
	understands that the ACD should be a reflection of the first Committee meeting and at the time of the meeting, the PAS for certolizumab pegol was under consideration by the Department of Health and therefore, the PAS was not considered within the Committee's preliminary recommendations. For the purpose of ACD 2, we would like to inform the Committee that the PAS for certolizumab pegol in axSpA has now been approved and is identical to the PAS already in place for rheumatoid arthritis; that is the first 12 weeks of treatment (ie. the first 10 vials) are provided at zero cost to the NHS. We would like to flag that the following sections of the ACD, mentioning the certolizumab pegol PAS, are affected and suggest they be updated accordingly as part of ACD 2/FAD: • Section 1.1 and Section 1.3: suggest the text indicate that "certolizumab pegol is recommended with or without a patient access scheme, where the first 12 weeks (10 pre-loaded 200 mg certolizumab pegol syringes) are provided at zero cost to all patients starting treatment".	FAD section 1.1).
	• Section 3.9: suggest the annual acquisition costs of certolizumab pegol be updated to reflect the agreed PAS. More precisely, suggest the text indicate that "Assuming the recommended dosage is followed (see section 3.7), the annual cost for the first year of treatment with certolizumab pegol is estimated at £10,367.50, reduced to £6,792.50 (including the agreed patient access scheme); for the maintenance year the cost of treatment is estimated at £9,295."	Comment noted. The price of certolizumab pegol is £357.50 for a 200 mg pre-filled syringe (excluding VAT; BNF edition 68). UCB Pharma has agreed a patient access scheme (PAS) with the Department of Health. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials. Assuming the recommended dosage is followed, the annual cost for first year of treatment with certolizumab pegol is estimated at £10,368 (or with the PAS £6793) (see FAD section 3.9).
	• Section 4.36: suggest the text be updated in the final guidance, stating that the certolizumab pegol costs with and without the PAS were considered.	Comment note. The Assessment Group's model used both the list price for certolizumab and the patient access scheme, so that the list price ICERs could be considered until the patient access scheme is agreed by the Department of Health (see FAD section 4.36).
	• Sections 4.39 – 4.44, within the table on p.37–40: suggest the base case results for certolizumab pegol be changed to be the one including the PAS.	Comment noted. See above.
	• Section 5.4: suggest the certolizumab pegol PAS also be described in Section 5.4 and in the	Comment noted. See above.

Consultee	Comment [sic]	Response
	table on p.70. **1.2 Certolizumab pegol Summary of Product Characteristics** In Section 3.7, p.9, it is stated that "The recommended induction dosage [for certolizumab pegol] for patients with ankylosing spondylitis…". In the summary of product characteristics (SPC) for certolizumab pegol, this initial dose is referred to as a "loading" dose, rather than an "induction" dose.1 UCB therefore request that the word "induction" is changed to "loading", to accurately reflect the SPC.	Comment noted. Certolizumab pegol is administered by subcutaneous injection. The recommended induction loading dosage for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 400 mg (given as 2 injections of 200 mg each) at weeks 0, 2 and 4 (see FAD section 3.9).
	In Section 3.8, "autoimmune conditions (including lupus-like syndrome)" is listed as an adverse reaction associated with certolizumab pegol treatment. The SPC for certolizumab pegol does not list autoimmune conditions as an adverse reaction, but rather it is stated that, "the impact of long-term treatment with Cimzia on the development of autoimmune diseases is unknown" and that, "there have been rare reports of other immune-mediated conditions; the causal relationship to Cimzia is not known".1 Lupus-like syndrome is listed as the only auto-immune disorder that has been associated with certolizumab pegol treatment and therefore we suggest the wording of the ACD in Section 3.8 be changed to list only lupus-like syndrome, rather than other autoimmune conditions.	Comment noted. The summary of product characteristics lists the following adverse reactions for certolizumab pegol: infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), blood and lymphatic system malignancies (including lymphoma and leukaemia), autoimmune conditions (including lupus-like syndrome), injection site reactions (erythema, itching, haematoma, pain or swelling), and hepatitis B reactivation (see FAD section 3.8).
	1.3 Description of the RAPID-axSpA trial **1.3.1 Recruitment of patients across the axSpA spectrum** Section 4.17 states: "The Assessment Group reported issues with 2 of the trials in nonradiographic axial spondyloarthritis (ABILITY-1 for adalimumab and Rapid-axSpA for certolizumab pegol), which were highlighted by the US Food and Drug Administration. These 2 trials included large proportions of people with ankylosing spondylitis." UCB would propose rewording Section 4.17 to the following: "The Assessment Group reported issues with 2 of the trials in non-radiographic axial spondyloarthritis (ABILITY-1 for adalimumab and Rapid-axSpA for certolizumab pegol), which were highlighted by the US Food and Drug Administration. These 2 trials were found to have discrepancy in classification of patients with non-radiographic axial spondyloarthritis or ankylosing spondylitis between local classification and central readings of X-rays. This was found to have an overestimation of the treatment benefit observed with TNF-alpha inhibitors in 1 of the trials (ABILITY-1). Rapid-axSpA was designed to include patients with ankylosing spondylitis or non-radiographic axial spondyloarthritis; misclassification did not impact the Rapid-	Comment noted. This section has been removed from the FAD.

Consultee	Comment [sic]	Response
	axSpA study results, with similar treatment effect regardless of how patients were classified." UCB considers the wording in the above mentioned section to be misleading in relation to the RAPID-axSpA trial. The RAPID-axSpA trial was designed to examine the efficacy of certolizumab pegol across the spectrum of patients with active axSpA, including both AS and nr-axSpA sub-populations. To enter the study patients had to have a physician diagnosis of axSpA, meet the ASAS classification criteria and have active disease plus the presence of objective signs of inflammation despite current treatment with NSAIDs, ie. the study recruited a cohort reflecting the label population. Recruited patients were then stratified into the AS and nr-axSpA subpopulations using the modified New York (mNY) criteria to ensure balance between the subgroups in each treatment arm. It is therefore misleading to state that the RAPID-axSpA study included a large proportion of AS patients when this group was recruited as per study protocol. As with historic AS registration studies, patients in the RAPID-axSpA trial were classified by a local investigator since this reflects how patients are diagnosed in clinical practice. A protocol amendment was later made to the study to conduct baseline X-rays of the sacroiliac joints, which were read centrally, to allow for an assessment of disease progression from nr-axSpA to AS to be performed at the end of the study. A discrepancy in classification of patients between the local investigator and central readers was found in the RAPID-axSpA study, with some patients classified as AS being reclassified as nr-axSpA and some nr-axSpA patients being reclassified as AS. However, this is a well-known phenomenon, reflects the unreliability of X-rays for classification and diagnosis, and is consistent with literature reports that also show a high degree of discrepancy between readers.2. Importantly, regardless of how patients were classified (by local investigators or according to the central read), the US Food and Drug Administration concluded that the treatment effect was the same, with the likelihood of achieving the primary endpoint of ASAS20 response not being dependent on whether patients had definitive evidence of sacroiliitis on X-ray.3 In light of this clarification, UCB feels that the above revised wording better reflects the differences in design of the 2 trials and the context of the analysis performed by the US Food and Drug Administration. **1.3.2 Objective signs of inflammation** In Section 4.58, it was stated: "The Committee noted comments from the Assessment Group that heterogeneity across the trials of nonradiographic axial spondyloarthritis may have confounded the outcomes for TNF-alpha inhibitors. The Committee heard from the clinical experts that these trials included people who were less likely to benefit from TNF-alpha inhibitors (people without objective signs of inflammation such as MRI changes and elevated C-reactive protein, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations". UCB considers that this statement is misleading, suggesting that all trials recruited some patients without objective signs of inflammation. UCB would like to clarify that the RAPID-axSpA trial recruited patients as per the UK marketing authorisation, that is, both AS and nr-axSpA patients had objective signs of inflammation, as determined by an elevated CRP measure or as detected by MRI.4 Patients with AS and nr-axSpA had comparable high disease burden at baseline and demonstrated a similar	Comment noted. No action required.

Consultee	Comment [sic]	Response
	treatment response to certolizumab pegol. UCB requests that the statement be revised to specifically highlight those trials that did include patients without objective signs of information. **1.4 Re-clarification of reporting of adverse events for anti-TNFs** In Section 4.21 it is stated: "When individual TNF-alpha inhibitors were analysed separately, only infliximab and certolizumab pegol were associated with statistically significant increases in adverse events compared with control treatments… certolizumab pegol was associated with higher rates of serious infections (NNH 12, 95% CrI 4 to 79) and serious adverse events (NNH 18, 95% CrI 9 to 162)." These conclusions are made with little context provided and make no mention of the limitations associated with the Cochrane review. The authors of the Cochrane meta-analysis acknowledge several limitations of their meta-analysis. Their findings are based on indirect comparisons and should be interpreted with caution because trials differed in patient populations, prior failed therapies, concomitant use of DMARDs, trial duration, and dose of biological; and event rates were often low.5 UCB request that additional context is added when the results of independent meta-analyses such as the Cochrane review are summarised, and refer to the limitations inherent in such analyses. Long-term safety of certolizumab pegol in axSpA has been shown to be consistent with other agents in this class. The absolute rate of serious infection events for patients treated with certolizumab pegol was similar to observations from other studies, which has been confirmed in a comprehensive pooled safety analysis including over 4,000 patients with rheumatoid arthritis, with over 9,000 patient years of follow up.6 Furthermore, the EPAR for certolizumab pegol states that in the RAPID-axSpA study, the adverse event profile of certolizumab pegol was as expected for TNF alpha inhibitors and consistent with previous experience for certolizumab pegol. No new safety signals were identified. Given the evidence highlighted above, UCB would request that additional context is provided to safety analyses, such as the Cochrane review, to provide a balanced and objective account of the safety profile of all agents.	Comment noted. No action required.
	1.5 Molecular structure of certolizumab pegol A brief overview of the various technologies are presented in Section 3. Although specific details regarding the molecular structure are provided in Section 3.1, UCB would request that additional clarification is provided for the structure of certolizumab pegol, which is highly different to the other monoclonal antibodies it is listed alongside. Certolizumab pegol is the only PEGylated Fab', Fc-free anti-TNF. The addition of the PEG part of the certolizumab pegol molecule increases the stability and half-life of certolizumab pegol, allowing the Fc-free molecule to have a similar half-life to a full antibody (14.4 days).7 PEGylation may also aid retention in inflamed tissue, and CZP has been shown to preferentially	Comment noted. No action required.

Consultee	Comment [sic]	Response
	accumulate in inflamed tissue in animal models. A study in naïve mice and mice with ongoing collagen-induced arthritis used fluorescently labelled CZP and ADA to show that both anti-TNF therapies achieved greater penetration into arthritic paws compared to normal tissue.8, 9 Although certolizumab pegol has not been approved for use in pregnancy,1 pre-clinical and clinical data suggest a lack of active placental transfer of certolizumab pegol which may be the consequence of the absence of an Fc region. Pre-clinical data showed that an anti-TNFα PEGylated Fab' fragment was undetectable or only detectable at a very low level in rodent foetal samples.10 An ex vivo placental transfer study found that in 6 human placentas, certolizumab pegol levels in the foetal circulation were consistently below levels of the anti-D IgG control.11 An independent investigator-driven study measuring placental transfer in 10 pregnant women treated with certolizumab pegol reported that certolizumab pegol levels in the cord blood and infant blood on the day of birth were consistently lower than those in maternal blood, suggesting low placental transfer. In some cases, certolizumab pegol levels in cord and infant blood were below levels of detection.12, 13 The European label for certolizumab pegol states that there are no adequate data from the use of certolizumab pegol in pregnant women.1 UCB would request that the wording around the certolizumab pegol molecule be revised to acknowledge its unique molecular structure, being Fc-free and PEGylated. **2 General responses** **2.1 Marketing authorisations**	
	In section 1.1 of the ACD, it is stated that "Adalimumab, certolizumab pegol, etanercept and golimumab are recommended within their marketing authorisations, as treatment options for active ankylosing spondylitis". We suggest this state "severe active ankylosing spondylitis", since this is the wording used in the summary of product characteristics of all the anti-TNFs (NB. this also applies to p.64).1, 14-16	Comment noted. Adalimumab, certolizumab pegol, etanercept, and golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (see FAD section 1.1).
	In section 1.3 of the ACD, it is stated that "Adalimumab, certolizumab pegol and etanercept are recommended within their marketing authorisations, as treatment options for non-radiographic axial spondyloarthritis". We suggest this state "severe non-radiographic axial spondyloarthritis", since this is the definition used in the SPC of all the relevant anti-TNFs.1, 14, 16	Comment noted. Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-

Consultee	Comment [sic]	Response
		inflammatory drugs (see FAD section 1.2).
	2.2 Treatment recommendations In Section 1.5, it is stated: "The response to adalimumab, certolizumab pegol, etanercept or golimumab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response". UCB would like to highlight that current clinical practice suggests an evaluation period between weeks 12 and 24 and would suggest that any treatment recommendations are validated with the ongoing updates to the British Society of Rheumatology clinical guidelines for axSpA. UCB would therefore suggest that the wording in this treatment recommendation be modified to offer more clinical discretion at the 12 week decision point.	Comment noted. The Committee discussed the response criteria used to determine whether TNF alpha-inhibitor treatment is continued in clinical practice. It heard from clinical experts that in UK clinical practice, response to TNF alpha-inhibitor treatment is usually assessed after 3 months. They defined an adequate response to treatment as an improvement in BASDAI score of at least 50%, or of at least 2 units. The experts explained that, in some people, the disease will not show a response to treatment until 6 months, but that most responses or partial responses occur within 3 months (see FAD section 4.53).
	2.3 The importance of extra-articular manifestations in axSpA In Section 1.4 it is stated: "The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, and may include consideration of associated conditions." UCB agrees that extra-articular manifestations are an important consideration when selecting an anti-TNF for the treatment of axSpA, given the frequency of extra-articular manifestations in such patients. To this point, UCB refers to the data provided in their original submission, indicating the efficacy of certolizumab pegol for the improvement of the symptoms of such manifestations of axSpA, including uveitis, enthesitis and extra-spinal joints (see Sections 5.48 and 5.4.9).17, 18 During the 24 week double-blind phase of RAPID-axSpA, the incidence rate of uveitis flares was lower in certolizumab pegol-treated patients than placebo-treated patients, both in the overall population and between patients with a history of uveitis at baseline. Incidence of uveitis remained low to Week 96. Certolizumab pegol-treated patients showed improvements in enthesitis, swollen joints and tender joints at Week 12 and Week 24 compared with placebo-treated patients, which were maintained to Week 96.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
	2.4 Sequential use of anti-TNFs in axSpA	

Consultee	Comment [sic]	Response
	Section 4.12 states: "The Assessment Group concluded that, despite a decrease in response rates, sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis." The Committee acknowledges the dearth of robust clinical evidence to support the use of sequential treatment with anti-TNFs, stating that the most compelling data are that from the DANBIO registry. UCB would like to reiterate that sequential use of anti-TNFs is likely to be beneficial to a number of axSpA patients. Data from other rheumatic indications show that many patients will eventually lose response to their first anti-TNF (secondary loss of response), likely due to anti-drug antibodies. These patients generally respond well to a second anti-TNF.19 Hence, a strong patient need exists for sequential use of anti-TNFs in axSpA, amongst those losing response to an initial anti-TNF to regain improvements in disease activity, given that there are no other approved treatment options once a patient has failed NSAIDs.	Comment noted. The Committee considered the clinical evidence for treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond or stops responding to treatment (sequential treatment). It agreed that, despite a decrease in response rates for each subsequent treatment, sequential treatment with TNF alpha inhibitors can be beneficial in ankylosing spondylitis (see FAD section 4.59).
	UCB further wish to highlight that limited data from the RAPID-axSpA study also suggest that the treatment response to certolizumab pegol is not different between anti-TNF naïve and experienced patients (anti-TNF experienced patients excluded patients with no initial response to an anti-TNF [ie. primary failure] but included patients who had discontinued an anti-TNF for reasons other than primary failure [eg. secondary failure]);20 ASAS40 responses and improvements in BASDAI scores were maintained on long-term in both anti-TNF naïve and experienced patients. While these results should be interpreted with caution given the low patient numbers in these analyses, they do add to the existing evidence base and support the efficacy of sequential treatment with anti-TNFs. UCB would request that the data covering sequential use of a second-line anti-TNF in the limited case of loss-of-response be re-considered.	Comment noted. No action required.
	2.5 Comment on the relevance of trial data to clinical practice In Section 4.14, it is stated: "When TNF-alpha inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10–16 weeks for all outcomes (Table 3). The Assessment Group reported that statistical heterogeneity was apparent in the analyses, and therefore the reliability of the pooled estimates, and their true relevance to people seen in clinical practice, is questionable. Estimates of the class effect of TNF-alpha inhibitors were consistently smaller in non-radiographic axial spondyloarthritis compared against those observed in ankylosing spondylitis trials".	Comment noted. No action required.
	UCB recognises the rationale for treating the anti-TNF agents as a single class, however, several comments related to this statement need to be considered: • The RAPID-axSpA trial is highly relevant to the UK clinical practice, being the only study to date to purposefully recruit across the spectrum of patients with active axSpA, including both AS and nr-axSpA sub-populations. The study design allowed for a direct comparison of baseline disease burden, quality of life and work-related productivity and treatment response between these sub-populations. Data from the RAPID-axSpA study showed a similar high disease burden and demonstrated comparable treatment effect between the AS and nr-	

Consultee	Comment [sic]	Response
	axSpA sub-populations.4 • It is also worth noting that in RAPID-axSpA, nr-axSpA patients were recruited with objective signs of inflammation (as defined by sacroiliitis on MRI and/or elevated CRP) in line with the licence population.4 We would therefore suggest that the wording in Section 4.14 be revised to acknowledge that the difference in treatment effect between AS and nr-axSpA subpopulations was not observed in all trials, for example: "Estimates of the class effect of TNF-alpha inhibitors were consistently smaller in non-radiographic axial spondyloarthritis compared against those observed in ankylosing spondylitis trials, except in the Rapid-axSpA trial, where a similar treatment effect was observed between patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis". **2.6 Comment on manufacturer ICERs** In Section 4.31, it is stated: "Although there was consistency across the companies' ICER estimates for the ankylosing spondylitis population, the Assessment Group considered them (and the ICERs reported for people with non-radiographic axial spondyloarthritis) to be both speculative and uncertain." While UCB acknowledge that generally ICERs are a result of modelling assumptions and subject to a level of uncertainty, and thus need to be tested through sensitivity analyses, UCB disagrees with the above comment on the speculative nature and high uncertainty of the ICERs. The uncertainty within the submitted models was explored through extensive sensitivity analysis, so although some uncertainty always exists within a model, this has at least been explored and quantified. Furthermore, the submitted models obtained remarkably similar ICERs for the AS subpopulation under differing assumptions in terms of rebound, BASDAI/BASFI progression and other structural modelling uncertainties. The observation that the York model provided similar ICERs also in the AS subpopulation serves as additional evidence for the robustness of ICERs under the numerous uncertainties. UCB request the Committee to revise their wording to reflect the consistency of the ICERs while reducing the emphasis that they are speculative and highly uncertain in the AS sub-population. **2.7 Accuracies in reporting the UCB cost-effectiveness model** **2.7.1 Week 24 response criteria** In Section 4.28, it is stated: "All models included response criteria to decide whether TNF-alpha inhibitors were continued or withdrawn. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, with the exception of company UCB which used response criteria at week 24." UCB would like to clarify that, as per our original submission, the Week 24 response criteria was only used as the base case assumption for the AS sub-population, and that a sensitivity analysis at Week 12 was conducted in order to explore this model assumption. For the nr-axSpA sub-population, a 12 week response criteria was used, reflecting the availability of data at this time point across the	Comment noted. Although there was consistency across the companies' ICER estimates for the ankylosing spondylitis population, the Assessment Group considered them (and the ICERs reported for people with non-radiographic axial spondyloarthritis) to be both speculative and uncertain (see FAD section 4.30). Comment noted. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, except for UCB Pharma which used response criteria at week 24, in its base-case model for the ankylosing spondylitis

Consultee	Comment [sic]	Response
	included clinical trials. UCB would therefore request this paragraph to be revised to accurately reflect the submitted evidence: "All models included response criteria to decide whether TNF-alpha inhibitors were continued or withdrawn. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, with the exception of company UCB, which used response criteria at week 24 for its base case model in the ankylosing spondylitis population."	population (see FAD section 4.27).
	2.7.2 Base case ICERs In Section 4.29, and Tables 6 and 7, p.30, ICERs for the anti-TNFs from the various manufacturer models are presented in both the AS and nr-axSpA sub-populations. UCB would request that the text in Section 4.29, and in Tables 6 and 7, be revised to highlight that the ICERs presented are from the base case analyses of AS and nr-axSpA submitted by manufacturers.	Comment noted. A comparison of the base-case ICER estimates compared with conventional therapy submitted by each company (see FAD section 4.29).
	2.7.3 Response criteria justification (AS) In Table 4, p.28, the response criteria justification for UCB's model is reported as "RAPID-axSpA primary". UCB would request this be updated to "RAPID-axSpA primary endpoint" to accurately reflect that the information refers to the study endpoint.	Comment noted. Table has been updated as suggested (See FAD Table 4).
	2.7.4 Annual rate of withdrawal (long-term) (AS) In Table 4, p.28, we would suggest that the Annual rate of withdrawal (long term) indicate that these are the assumptions applied to all anti-TNFs in each model, to make a clear distinction between the models developed by AbbVie, MSD and UCB, from the assumptions made by Pfizer, which was applied to etanercept only.	Comment noted. Table has been updated as suggested (See FAD Table 4).
	2.7.5 Model type (nr-axSpA) In Table 5, p.29, the model type presented for UCB's model is "Markov model". UCB would request this be revised to "Decision tree followed by Markov model" to accurately reflect the evidence from the UCB original submission.	Comment noted. Table has been updated as suggested (See FAD Table 5).
	References 1. European Medicines Agency. Summary of Product Characteristics (Cimzia). Last updated 19/01/15. 2. van Tubergen A, Heuft-Dorenbosch L, Schulpen G, et al. Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? Ann Rheum Dis.	

Consultee	Comment [sic]	Response
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Consultee	Comment [sic]	Response
	16. European Medicines Agency. Summary of Product Characteristics (Enbrel). Last updated 28/05/15. 17. Rudwaleit M, Landewé R, Marzo-Ortega H, et al. Observed incidence rates of uveitis following certolizumab pegol treatment in patients with axial spondyloarthritis. Abstract SAT0355. Ann Rheum Dis. 2014;73(Suppl 2):721-722. 18. Mease P, Dougados M, Davies O, et al. Certolizumab pegol rapidly reduces peripheral enthesitis and the incidence of tender and swollen joints in patients with active axial spondyloarthritis, including both ankylosing spondylitis and non-radiographic axial spondyloarthritis. Abstract SAT0362. Ann Rheum Dis. 2014;73(Suppl 2):724-725. 19. Lloyd S, Bujkiewicz S, Wailoo AJ, et al. The effectiveness of anti-TNF-α therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. Rheumatology. 2010. 20. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. Arthritis Rheumatol. 2015;67(3):668-77.	

Comments received from commentators

Commentator	Comment [sic]	Response
Healthcare Improvement Scotland	Comment provided to Healthcare Improvement Scotland by Dr [redacted], Senior Lecturer in Rheumatology, University of Glasgow Comments on the NICE ACD We welcome this ACD, which is overall very thorough and consistent with clinical practice in Scotland. The only significant discrepancy and clinical issue is the specific recommendation against sequential use or switching to another TNF inhibitor in those who have failed to respond or lost efficacy with their first TNFi (Section 1.6 in the ACD). There is currently no SIGN guidance for AS/axSpA, while the SMC advice for the specific agents either does not comment on switching or includes the line “"Switching to a second TNF blocker might be beneficial especially in patients with loss of response”. In clinical practice, most rheumatology centers in Scotland have been switching appropriately selected patients with AS to subsequent TNFi with good effect and response. These decisions are made on an individual-by-individual	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5)

Commentator	Comment [sic]	Response
	basis with efforts made to exclude other causes of pain or failure to first TNFi (eg fibromyalgia, mechanical back pain) and include repeat imaging to confirm objective evidence of “inflammation”. This has been in line with the ASAS and EULAR guidelines. We are also aware if the anxiety the inability to switch in England has caused patients and clinicians (also commented on in ACD 4.24 & 4.54), and that this has often resulted in patients remaining on an ineffective/partially effective first TNFi rather than switching to a more effective subsequent TNFi. We acknowledge that the published evidence for switching is limited, and that RCTs for this are unlikely to ever be performed; however, the data from observational studies (eg DANBIO commented on in section 4.12) and clinical experience supports switching and is reflected in the comments in the ACD in sections 4.12 (The Assessment Group concluded that, despite a decrease in response rates, sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis) and 4.59 (The Committee concluded that sequential treatment with TNF-alpha inhibitors is likely to be beneficial, but that clinical data are limited). The decision to specifically not recommend sequential use is therefore based on insufficient cost-effectiveness evidence to allow it to recommend sequential use of TNF-alpha inhibitors as a cost-effective use of NHS resources (4.69) although the Assessment Group had not modelled sequential use (4.49). This specific recommendation against switching would therefore be a retrograde and negative step for patients in Scotland. If the committee feels unable to recommend sequential use due to lack of evidence, then there should not be any specific recommendation relating to this, rather than specifically recommending against switching. Comments using the specific headings: 1. Do you consider that all the relevant evidence has been taken into account? Overall very thorough, but it does not appear that all data about sequential use of TNFi has been taken into account (see also above). Specifically, there is more data supporting the effectiveness of switching between TNF inhibitors in ankylosing spondylitis in the NOR-DMARD register (Lie et al Ann Rheum Dis 2011;70:157-63) and the ATTRA register (Pavelka et al Rheumatologica 2012;50:294-306). 2. Do you consider that the analysis of clinical and cost effectiveness has used	Comment noted. See above. The Committee considered the clinical evidence for treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond or stops responding to treatment (sequential treatment). The Committee noted the absence of randomised controlled trial data, but noted data from the DANBIO registry for ankylosing spondylitis and comments received on the appraisal consultation document identifying other registries

Commentator	Comment [sic]	Response
	an appropriate comparator which reflects Scottish practice? Yes	and studies, including ATTRA, NOR-DMARD, RAPID-axSpA and RHAPSODY. It agreed that, despite a decrease in response rates for each subsequent treatment, sequential treatment with TNF-alpha inhibitors can be beneficial in ankylosing spondylitis (see FAD section 4.59).
	3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? Yes	Comment noted. No action required.
	4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? See above comments about switching	
	5. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? Generally yes, apart from the above comments about switching/sequential use.	Comment noted. No action required.
	6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? Overall unlikely to be significant change in numbers. Most specialist units are already treating non-radiographic axSpA in line with the licensing, SMC and ASAS guidelines (mentioned in the SMC advice). There would however be a negative impact on selected patients if switching were no longer allowed (see above)	Comment noted. No action required.
	7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? Yes. While most recommendations are consistent with current practice, the recommendation not to switch patients (section 1.6) would have negative implications on patients with ongoing active and severe disease.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response

Commentator	Comment [sic]	Response
		(see FAD section 1.5)
Healthcare Improvement Scotland	Comment provided to Healthcare Improvement Scotland by [redacted], Consultant Rheumatologist	
	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? Yes, involved all relevant stake holders and considered scientific evidence and listened to patient experiences.	Comment noted. No action required.
	2. Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice? If not, please explain. We follow British society for rheumatology guidance in the management of many rheumatological disorders including AS therefore there is no difference in the initial management of ankylosing spondylitis and comparator is same in Scotland. Non radiographic spondyloarthropathy is recently recognised entity and there are no specific guidelines resulting in potential differences but all the evidence and my discussions with colleagues in England did not reveal widely differing practice and therefore comparator used is appropriate.	Comment noted. No action required.
	3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? Agree	Comment noted. No action required.
	4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? Yes, however I would prefer some more clarity on recommendation 1.4 “if more than one treatment is suitable, the least expensive should be chosen” This can be interpreted as using drug with low cost as most anti TNF agents are suitable in AS and nr-SpA but that particular drug may not be the most suitable agent for that patient – as clarified in 4.70.	The choice of treatment should be made after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This may include consideration of associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen (see FAD section 1.3).

Commentator	Comment [sic]	Response
	5. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Yes. Etanercept is not approved by SMC for nr-SpA in Scotland where as Adalimumab and Certolizumab are approved. These recommendations however are going to bring Etanercept in to the group.	Comment noted. Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. (see FAD section 1.2).
	6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. No. Eventhough one more drug is going to be included in the armamentarium it is not for a new indication therefore unlikely to increase patient numbers significantly.	Comment noted. No action required.
	7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. No	Comment noted. No action required.
	8. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment Not every AS patient responds to the treatment at the same speed and there is small but significant proportion where anti TNFs appears effective at 6 months and is acknowledged in the report. Given the lack of sequential treatment options (another anti TNF or otherwise) for this particular group of patients it may be worth continuing treatment up to 24 weeks rather than recommended 12 weeks but only in those who are showing some improvement for e.g. 25% improvement in BASDAI or improvement by 1 or more units. I am not sure if such scenario is taken in to calculations of cost effectiveness but as these patients are very small in numbers unlikely to have huge cost effect.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5)

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional England		The recommendations in 1.5 and 1.6 state: 1.5 For people who cannot tolerate adalimumab, certolizumab pegol, etanercept or golimumab and who stop taking it before response can be assessed at 12 weeks, another TNF-alpha inhibitor is recommended within its marketing authorisation. 1.6 Treatment with another TNF-alpha inhibitor is not recommended for people whose disease has not responded to treatment with the first TNF-alpha inhibitor, or those who had an initial response which was then lost. These statements do not accomodate a patient who develops an intolerance to an anti-TNF after the intiial 12 week assessment. 1.5 suggests that this indication is not covered BUT 1.6 does not specifically relate to intolerance occuring beyond 12 weeks; it just relates to "non-responders" and those who had an "intitial response which was then lost". We have had a request for such a patient that developed intolerance beyond 12 weeks and it would be helpful if NICE could clarify the position for this group of patients. This is a common problem with many NICE TA's which often leave too many "grey areas" which require local interpretation.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
	Disclosure	Thank you No	

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
Administrator o Primary Cre Rheumatology Society England		In general, we welcome the conclusions of the ACD, especially the extension of the use of TNF-alpha inhibitors to treat non-radiographic axial spondylarthropathy. However, we are concerned at recommendation 1.6 Treatment with another TNF-alpha inhibitor is not recommended for people whose disease has not responded to treatment with the first TNF-alpha inhibitor, or those who had an initial response which was then lost• . We note that the Committee considered the evidence for sequential use of another TNF-alpha inhibitor, and the conclusions contained in section 4.59. We note the conclusion that sequential treatment with TNF-alpha inhibitors is likely to be beneficial, but that clinical data are limited. It is our opinion that this conclusion could discriminate against people with ankylosing spondylitis compared with people with rheumatoid arthritis, another auto-immune rheumatological disorder. NICE TAG195 allows sequential treatment with TNF-alpha inhibitors in patients with RA who have not responded to a first TNF-alpha inhibitor, or whose initial response has been lost. In order to achieve equality between patient groups, we feel that sequential treatment should be considered in these circumstances. Response written by [redacted], Steering committee member, Primary Care Rheumatology Society.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
	Disclosure	No	

Role*	Section	Comment [sic]	Response
Patient		I am writing with regards to the Appraisal Committee's preliminary recommendations, Section 1 - point 1.6 titled 'Treatment with another TNF- alpha inhibitor is not recommended for people whose disease has not responded to treatment with the first TNF-alpha inhibitor, or those who had an initial response which was then lost': I am a young female of 30 years, who sufferers terribly with Ankylosing Spondylitis. I am currently on my first TNF blocker drug Golimumab, and have been so for over a year now. I have not responded particularly well to the drug - and i've suffered with re-current infections. My consultant Dr [redacted] is keen to move me to another TNF blocker, one which i take more regularly, with the view that it will give me more coverage. Therefore, i am outraged to read of your desire to remove this opportunity from patients like myself. Your report states that the response rates and benefits are reduced with 2nd and 3rd anti tnfalphas , yet the evidence provided does not in any way seem robust enough to support such a bold claim. Furthermore, I know of thousands of patients who attend NASS members days annually who share such glorifying stories of successes with a 2nd TNF blocker. We know that all TNF blockers work in different ways, so why should it be a lucky dip for sufferers to get the right drug first time round? Beyond the statistics, i can tell you first hand that the reality of living with this chronic condition is bleak. Your preliminary decision to remove the right to try a second TNF after the 12 week window has past leaves sufferers like myself in absolute dismay. I am a young woman who dreams of a family one day - but without the right treatment, it is only a matter of time before i am forced to stop working, and left unable to live the life i rightly deserve. I urge you to reconsider this decision - it will leave young sufferers like myself with no hope at all.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
	Disclosure	N/A	

Role*	Section	Comment [sic]	Response
Patient England		I think the following are a positive move forward: 1) Offering four types of anti-TNF to patients 2) Using MRI results and not just X-ray results to make the decision to offer anti-TNF. This will enable earlier diagnosis and effective treatment plans to be made.	Comment noted. No action required.
		The negatives of this report for me as an AS sufferer are: 1) Not being offered a different anit-TNF if the one you have tried does not work or stops working. I think this is short sighted because people respond to medications in different ways. Surely the aim is to help patients find the treatment that works best for them, even if it means trying out a few in the process. The long term gain for this would be far higher than the short term cost saving. Anti-TNF medication literally changes the quality of someone's life so patients should be given options regardless of whether they have tried one type of anti-TNF or not.	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
	Disclosure	2) Patients should be offered MRI scans more regularly. I have only had one and that was 6 years ago. If my treatment plan is being aided by MRI results, surely you will need more updated results to see how the disease is progressing / not No	Comment noted. No action required.
Pharmaceutical Industry England		We query why the patient access scheme for certolizumab pegol has not been mentioned within Section 1.1 of the appraisal consultation document of TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis [ID694]. Our interpretation of this is that certolizumab pegol is recommended in ankylosing spondylitis and non-radiographic axial spondyloarthritis even without the patient access scheme? We note that in the Rheumatoid Arthritis appraisal consultation document [ID537] the discount agreed in their patient access schemes is referred to for certolizumab pegol, golimumab, abatacept and tocilizumab at Section 1.1	Comment noted. The price of certolizumab pegol is £357.50 for a 200 mg pre-filled syringe (excluding VAT; BNF edition 68). UCB Pharma has agreed a patient access scheme (PAS) with the Department of Health. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials (see FAD section 3.9).
	Disclosure	N/A	
NHS Professional England		We are a group of clinicians working in the field of spondyloarthritis and conduct a large specialist clinic providing tertiary care for over 600 people with axial SpA. We have used TNF inhibitors (TNFi) for this condition for the last 15 years after conducting the first interventional studies worldwide looking at the efficacy of these agents. As such, our	

Role*	Section	Comment [sic]	Response
		experience with both the disease area and the use of these drugs is vast and recognized at international level. We would like to comment on the eagerly anticipated appraisal consultation document (ACD) TNF alpha inhibitors (TNFi) for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA 233). We welcome the majority of the conclusions, in particular the treatment of those individuals who suffer from axial SpA on its non-radiographic form as they represent a neglected group with no treatment options up to now.	
		We are, however, extremely concerned about the ACD positioning on the recommendation of switching or treatment with another TNFi for those people whose disease has not responded to treatment with the first TNFi, or those who had an initial response which was then lost (1.6). In particular, we feel that the available evidence does not support this statement, rather the opposite. We would like to highlight the following	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
		1. Switching is cost-neutral in real life. We believe that there are other interpretations to the data outlined on Point 4.32 (Page 32) which discusses the model presented by Pfizer on pairwise comparison of TNFi versus conventional care. This, in our opinion, is not ideal as there is no such a thing as conventional care in axSpA. Conventional care in axSpA refers to physiotherapy and NSAID use which has limited evidence beyond symptomatic relief. Risk of cardiovascular, renal and gastrointestinal toxicity is substantial. There are a paucity of data on the long term impact of NAIDs. Once the decision to start a biologic drug is made, it is assumed that an expense will be incurred and this will continue. This is so as current data suggest that drug free remission is unlikely with the majority experiencing a relapse that will require re-starting treatment. Whether this is the initial agent or a new one, the cost will vary minimally and it is assumed to be nearly equal. This is particularly so, since infliximab is currently not supported by NICE. As such switching in axial SpA is cost-neutral.	
	Disclosure	The Rheumatology Department at LTHT conducts clinical trials sponsored by pharmaceutical companies who manufacture biologic treatments for people suffering with axial Spondyloarthritis.	Commented noted. No action required.

Summary of comments received from members of the public

Theme	Response
Sequential use of TNF-alpha inhibitors not recommended in draft guidance	Comment noted. Treatment with another tumour necrosis factor (TNF) alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF alpha inhibitor, or whose disease has stopped responding after an initial response (see FAD section 1.5).
Pleased that TNF-alpha inhibitors recommended for the treatment of non-radiographic axial spondylarthropathy	Comment noted. Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (see FAD section 1.2).
Four TNF-alpha inhibitors have been recommended for ankylosing spondylitis	Comment noted. Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop (see FAD section 1.1).
Patients should be offered MRI scans more regularly	Comment noted. No action required.
The certolizumab patient access scheme was not included in the draft recommendations.	Comment noted. The price of certolizumab pegol is £357.50 for a 200 mg pre-filled syringe (excluding VAT; BNF edition 68). UCB Pharma has agreed a patient access scheme (PAS) with the Department of Health. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials (see FAD section 3.9).