National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

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Background information	AbbVie	It is stated in the background section that : *"If definite sacroiliitis is absent on radiography, the disease is classified as axial undifferentiated spondyloarthritis."* AbbVie notes that axial spondyloathritis and undifferentiated spondyloarthropathy are two different conditions. If definitive sacroilitis is absent on radiography but the patient shows evidence of inflammation on MRI or their clinical features correlate, the disease is classified as non-radiographic axial SpA. It is also stated in the background information that: *"In ankylosing spondylitis […] Other joints of the body may also be involved, and the eye, bowel and cardiovascular system can be affected."* AbbVie notes that skin can also be affected In ankylosing spondylitis. It is further stated that: *"Ankylosing spondylitis […] is nearly 3 times more common in men than in women".* AbbVie notes that for completeness it should be mentioned that non-radiographic axial SpA affects approximately equal numbers of men	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the scope has been amended to remove any factual inaccuracies raised during consultation.

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		and women. It is further stated that: *"Conventional therapy includes [...] disease-modifying drugs (DMARDs)"* AbbVie notes that DMARDS should not be considered conventional therapy for Ankylosing Spondylitis and non-radiographic axial SpA. DMARDS can be recommended for the treatment of peripheral disease only according to axial SpA clinical guidelines (e.g. the current ASAS/EULAR guidelines for the management of AS mention that "Sulfasalazine may be considered in patients with peripheral arthritis.")	
	ARUK	The delineation of ankylosing spondylitis and axial spondyloarthritis is not clear. In reality, it is now recognised that a spectrum of disease exists in which there is spinal inflammation, almost invariably with sacroiliac joint inflammation. However, at one end of this spectrum inflammation of the sacroiliac joints is demonstrable only by MRI scanning, the X-ray appearances being normal, whilst further along the spectrum changes to sacroiliac joint X-rays occur. Some patients develop extensive X-ray changes in the sacroiliac joints and spine whilst others have non-radiographic disease. The whole spectrum is referred to as axial spondyloarthritis. This is the nub of the classification published by ASAS and described in the literature[1-3]. The notion that the primary lesion is in the sacroiliac joints with inflammation "rising up the spine" may also be misleading. It is true that in many instances this is the case and recognition of sacroiliac joint inflammation is a key diagnostic element. However, patients may present with inflammatory changes elsewhere in the spine, which may be painful and disabling, in spite of limited or normal appearances of the sacroiliac joints. The statement that "it is characterised by mild to moderate flares of	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the scope has been amended to remove any factual inaccuracies raised during consultation.

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		active disease ….” is curious. For some patients, symptoms are extremely severe and disabling and fluctuations in intensity of symptoms may also be severe and disabling. The notion that this is at worst a moderate disease belittles the extent to which many patients suffer. The statement that “occasionally the disease is severe …” requires modification. Severe instances are considerably more than occasional. A crucial element of the severe bony changes in the spine is that they are irreversible. They cannot, therefore, be compared in any way with peripheral joint abnormalities which may be amenable to surgical amelioration. Overall, in axial spondyloarthritis, the male to female ratio is approximately 1 to 11. It is true that in ankylosing spondylitis, that is, in patients with radiographic abnormalities, males predominate; however, when patients with non-radiographic disease are included, the ratio is close to unity. This is because radiographic changes are less likely to occur in women even though symptoms and functional impairment may be comparable. The review of available treatments implies that a range of treatments including local corticosteroids and disease-modifying drugs are available for both axial and peripheral disease. These are used for the treatment of peripheral disease, although the evidence base is slight, but are not effective for axial disease. This is critically important, as the available treatments for axial disease are therefore physiotherapy, NSAIDs and tumour necrosis factor-α inhibitors. 1.Rudwaleit M1, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, Braun J, Chou CT, Collantes-Estevez E, Dougados M, Huang F, Gu J, Khan MA, Kirazli Y, Maksymowych WP, Mielants H, Sørensen IJ, Ozgocmen S, Roussou E, Valle-Oñate R, Weber U, Wei J, Sieper J. The development of Assessment of SpondyloArthritis international	

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		Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009; 68:777-83. 2. Sieper J and van der Heijde D Nonradiographic Axial Spondyloarthritis; New Definition of an Old Disease? ARTHRITIS & RHEUMATISM 2013;65:543–551 3. Isdale A, Keat A, Barkham N, Bennett AN, Gaffney K, Marzo-Ortega H, Sengupta R. Expanding the spectrum of inflammatory spinal disease: AS it was, as it is now. Rheumatology 2013;52:2103-5	
	British Society for Rheumatology (comment endorsed by the Royal College of Practitioners)	1. The term “axial undifferentiated spondyloarthritis” is incorrect. A summary of the classification system for the disease area is outlined in the following publications/editorials: Expanding the spectrum of inflammatory spinal disease. AS it was, as it is now. Isdale A, Keat A, Barkham N, Bennett A, Gaffney K, Marzo-Ortega H, Sengupta R. Rheumatology 2013;52:2103-5. Nonradiographic axial spondyloarthritis – new definition of an old disease. Sieper J, van der Heijde D. Arthritis Rheum 2013; 65: 543-51. 2. In AS, inflammation does not necessarily rise up the spine – it is often diffuse and axial/spinal disease can precede sacroiliitis. 3. DMARDs are ineffective in spinal disease therefore they do not form part of conventional therapy. Established practice is NSAIDs and physiotherapy prior to considering anti-TNF. 4. The concept of AS being a disease characterised by “mild or moderate flares” is untrue and misleading. This statement underestimates the severe and disabling symptoms that many patients endure. 5. The definition of severe disease needs to be clarified. 6. The gender difference in non-radiographic axial SpA is 50:50 rather	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the scope has been amended to remove any factual inaccuracies raised during consultation.

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		than being male dominated. In AS there is a male preponderance 1. Rudwaleit et al. Arthritis Rheum 2009:60;717–727. 2. Haibel et al. Arthritis Rheum 2008;58:1981–1991. 5. van der Heijde et al. Arthritis Rheum 2006;54:2136–2146. 6. Davis et al. Arthritis Rheum 2003;48:3230–3236. 7. van der Heijde et al. Arthritis Rheum 2005;52:582–591. 8. Inman et al. Arthritis Rheum 2008;58:3402–3412. 9. Rudwaleit et al. Ann Rheum Dis 2009;68:777–783.	
	National Ankylosing Spondylitis Society (NASS)	Axial spondyloarthritis versus ankylosing spondylitis The distinction between axial spondyloarthritis and ankylosing spondylitis does not seem to be very clear in the scope document. NASS have defined it in our patient information as follows: 'Axial Spondyloarthritis or axial SpA for short (abbreviated as axSpA) refers to inflammatory disease where the main symptom is back pain, and where the x-ray changes of sacroiliitis may or may not be present. Within this axial SpA group, there are 2 subgroups: 1. Ankylosing Spondylitis (AS) - this is the diagnosis when the x-ray changes are clearly present. 2. Non-radiographic axial spondyloarthritis (nr-axSpA) - this is the diagnosis when x-ray changes are not present but clinical symptoms may occur. During this time, up to 70% of patients may have visible inflammation in the sacroiliac joints and/or the spine when an MRI of the back is done. But the other 30% may not have any change visible on the MRI despite clinical symptoms of back pain. In fact some of these patients may never show any inflammation on an MRI even if this is repeated later on in life. The reasons for this are not very clear and they may have to do with how good or sensitive our methods to image the	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the scope has been amended to remove any factual inaccuracies raised during consultation.

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		joints really are.' 'In ankylosing spondylitis, sacroiliitis is present and this inflammation rises up the spine' This is not an accurate description of ankylosing spondylitis. It is a very variable condition and not all people with ankylosing spondylitis conform to the norm. Not every patient has sacroiliitis and, additionally, people can have sacroiliitis and inflammation or fusion in the cervical spine or thoracic spine – rather than the inflammation rising up the spine. 'Occasionally the disease is severe' The term 'occasionally' is misleading. Data shows that up to 25% of people with ankylosing spondylitis eventually develop complete fusion of the spine which leads to substantial disability and restriction. NASS conducted a survey of 1630 people with ankylosing spondylitis in August 2013. The data shows that when using a scale of 1 to 10 where 1 represented 'not severe at all' and 10 represented 'very severe', people estimated the severity of their ankylosing spondylitis at an average 5.41. 23.2% estimated the severity of their ankylosing spondylitis as being 8, 9 or 10. 'It is characterised by mild or moderate flares of active disease' Flares ups are commonly severe and can be disabling. People tell us they are not able to get out of bed when they have a flare up or it might take 2-3 hours to be able to start moving. A flare up might mean people cannot look after their children, go to university or to work. Flare ups have a major impact on people's lives. 'may require joint replacement surgery for some patients' In the NASS survey as detailed above 10.8% had experienced joint replacement surgery and a further 4.1% were in need of joint replacement surgery.	

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		Of the 10.8% (168) who had joint replacement surgery, 71.1% had hip replacement, 8.8% hip resurfacing, 25% had knee replacement and 10.7% had shoulder replacement. Is the term 'may require' sufficient to cover nearly 15% of patients? It is nearly 3 times more common in men than in women' This is inaccurate. Currently it is estimated and data suggests that the proportion of men and women developing axial spondyloarthritis is more or less equal. 'Conventional therapy includes.....disease-modifying drugs (DMARDs)' There is no evidence that sulfasalazine or methotrexate are effective in treating spinal inflammation. These drugs are only utilised for patients who additionally suffer with peripheral symptoms. DMARDs should therefore not be classed as 'conventional therapy'. 'it does not recommend infliximab for ankylosing spondylitis' For the sake of clarity it should be made clear that this recommendation was made on the grounds of cost and was not based on efficacy.	
	Pfizer	Pfizer point out that the terminology of disease classification used in the scope should reflect the licences of the technologies being appraised. The Background of the draft scope states: "If definite sacroiliitis is absent on radiography, the disease is classified as axial undifferentiated spondyloarthritis." This does not match the anticipated wording of the license for etanercept which states: Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to conventional therapy. The third paragraph states: "The course of the disease varies among patients. It is characterised by	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the

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		mild or moderate flares of active disease alongside persistent symptoms. Occasionally the disease is severe leading to spinal fusion and significant deformities that may require joint replacement surgery for some patients." Pfizer point out that patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA), can present with a range of symptoms. Available information for AS indicates many patients can suffer from a severe course of disease (Zink et al, 2000). The fifth paragraph of the background states: "Conventional therapy includes acute anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and local corticosteroids, disease-modifying drugs (DMARDs, such as sulfasalazine and methotrexate) and physiotherapy." Pfizer make the point that as part of conventional treatment, patients may receive multiple therapies. Clinical input on the relevance of these therapies to UK clinical practice should be sought during the appraisal.	scope has been amended to remove any factual inaccuracies raised during consultation.
	Royal College of Nursing	The information provided is comprehensive and takes in the range of diseases incorporated under the umbrella of spondyloarthropathy. The predominant feature is "inflammatory back pain". Currently the scope states just "back pain" which is too generic a term. In paragraph 3 where it is stated that flares are mild to moderate, patients often report severe flares and this should be reflected. Severe flares do not always co-relate with severe disease progression and patients may not have spinal fusion. The ratio of male to female tends to change with age and in the early years some studies suggest that it is 1:1 ratio. This variation may reflect the progression to severe disease which is more typical in men. Infliximab is known to be very effective in the treatment of Ankylosing Spondylitis (AS) however cost is the limiting factor as it is weight related	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the scope has been amended

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		and can cost significantly more than the home administered options. However it is useful to have it considered if individuals have either adverse reaction or are secondary non responders to the home self-injection options.	to remove any factual inaccuracies raised during consultation.
	UCB	In the background section of the document UCB would suggest to clarify several important points relating to the concept of axial Spondyloarthrits. 1. Definition of axial Spondyloarthritis Paragraph 2: Clarify that axSpA is not simply "chronic back pain" (See below). Also paragraph 3 is focused on AS, suggesting that extra-spinal manifestations are only observed in AS patients. These points are equally relevant to axSpA occurring with similar frequency across the axSpA disease spectrum and are helpful in diagnosing the disease. We would suggest clarify as below: Patients with axSpA is a chronic inflammatory disease which can be distinguished from non-inflammatory causes of back pain based on a combination the presence of following signs and symptoms: inflammatory back pain, peripheral symptoms (arthritis, enthesitis, dactylitis), extra-articular manifestations (i.e. uveitis, IBD, psoriasis); the genetic marker human leukocyte antigen (HLA)-B27; the presence of signs of inflammation (i.e. C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]); imaging evidence of inflammation on MRI of the SI joints, or structural damage on the radiographs of the SI joints (AS patients). 2. Rationale for the development of the axSpA concept. In paragraph 4 the ASAS classification criteria are mentioned, but there is no discussion as to why the classification criteria were developed and why the field is embracing axSpA and moving away from AS. We should suggest that this point is clarified as discussed below.	Comments noted. The background of the scope is only intended to provide a brief overview of the condition and current treatment options. More detailed information will be included in the evidence submissions from the manufacturers and in the Assessment Report. The background of the scope has been amended to remove any factual inaccuracies raised during consultation.

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		Historically, patients with axSpA were only identified when there was evidence of structural damage in the SI joints on x-ray (according to the modified New York [mNY] criteria). i.e. when they had AS. However, advances in the understanding of axSpA have highlighted that some patients have clinical manifestations before radiographic sacroiliitis is apparent (nr-axSpA). Therefore, both AS and nr-axSpA represent the spectrum of axSpA, with the presence or absence of radiographic sacroiliitis as the only differentiating clinical feature. Additionally, using radiographs to make a diagnosis of axial SpA creates several challenges. Structural changes may take many years to develop (if at all) which resulted in a long delay in diagnosis (typically 5-10 years). Finally, there is a great deal of variability in the interpretation of SIJ x-rays when assessing sacroillitis. The availability of MRI has facilitated visualisation of inflammatory changes before structural changes occur on x-rays. Importantly, patients with nr-axSpA and AS have the same clinical features and level of disease actvitiy (e.g. BASDAI) and pain independently of whether they are classified as having nr- axSpA or AS 3. Burden of Disease There is currently no mention of the relative burden of disease in axSpA. Given that it is disease burden, in terms of signs and symptoms, that drives treatment choices in axSpA, it is helpful to clarify how the disease burden compares between AS and nr-axSpA. Given that the ASAS classification criteria for axSpA are relatively new, most data on the burden of disease for axSpA therefore relate to AS and fewer data are available on the nr-axSpA sub-population or the wider axSpA population. Data from a European cohort (German Spondyloarthritis Inceptions Cohort) demonstrated that axSpA has a deleterious effect on patients regardless of the presence (AS) or absence (nr-axSpA) of evidence of sacroiliitis on radiographs. Several studies have identified that the	

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		burden of subjective symptoms (e.g. pain, perceived disease activity, fatigue) is comparable in nr-axSpA and AS patients, although spinal mobility and functional status (BASFI) are usually somewhat worse in AS than in nr-axSpA due to the presence of structural damage in the former patient group. The burden of axSpA disease has frequently been found to be similar between AS and nr-axSpA, with similar scores reported on the SF-36 quality of life instrument. Nearly a third of patients with AS suffer from severe pain and patients with nr-axSpA have similar pain levels and experience similar fatigue to those with AS. In addition to the negative effects experienced by patients, axSpA represents an economic and social burden, with significant drug costs and decreased work productivity. Previous studies of the economic burden have focused on AS and the specific economic burden associated with nr-axSpA is yet to be comprehensively investigated. However, observations that nr-axSpA patients are comparable to AS patients in terms of reported health status, disease activity, and physical function, suggest that it could be expected that once adjusted for disease duration, costs could be similar. Furthermore, a recent study estimated the economic burden of axSpA, AS and nr-axSpA, in terms of paid work and household productivity, The findings of this study indicated that there was a similarly high burden of disease on workplace and household productivity between AS and nr-axSpA patients that could lead to a large financial burden for patients and society. Further to the above clarifications on the disease background, UCB would like to comment on some Inaccuracies mentioned in the Background section: - “Inflamed on radiography”: x-rays measure structural changes as the result of inflammation, not inflammation. This is the reason for the	

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		ASAS group developing the axSpA classification criteria to utilise the advantages of MRI imaging to detect inflammation in the SIJ joints before structural changes occur to facilitate earlier recognition and diagnosis of patients. Furthermore, structural changes will not occur in all patients despite persistent SIJ inflammation. - "axial undifferentiated spondyloarthritis" is not an established term. The term, as per ASAS definitions and European labels, should be non-radiographic axSpA (nr-axSpA) or axial spondyloarthritis without radiographic evidence of AS. -"New criteria for the diagnosis of axSpA have been developed": ASAS criteria are classification criteria to facilitate the earlier recognition of homogeneous groups of patients for clinical studies. While they can help inform a diagnosis, they are not diagnostic criteria.	
The technology/ intervention	AbbVie	The technologies are accurately described.	Comment noted. No changes required.
	ARUK	Yes [*Is the description of the technology or technologies accurate?]*	Comment noted. No changes required.
	British Society for Rheumatology (comment endorsed by the Royal College of Practitioners)	It is crucial to consider sequential treatment and drug survival in patients with AS. There is currently no option to "switch" under existing guidance. These patients do not have the option of alternative therapies.	Comment noted. Consideration of the optimal sequencing of TNF inhibitors has been proposed as a subgroup analysis if the evidence allows.
	Merck Sharp and Dohme	MSD would like to clarify that studies of golimumab for axial spondyloarthritis are still ongoing. There are no completed trials for golimumab in this indication.	Comment noted. The Committee will consider all available evidence during the course of the appraisal.

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	Pfizer	Paragraph 2 contains a typographical error: "Certolizumab pegol is licensed for the treatment adults..." should read: "Certolizumab pegol is licensed for the treatment of adults..."	Comment noted. The scope has been amended in line with the suggested change.
	Royal College of Nursing	The technologies appear to have been described accurately.	Comment noted. No changes required.
	UCB	Whilst the description of the technologies is accurate we would ask NICE to confirm the comparators and specifically ensure the licence restrictions are reflected. We understand that only comparators currently licensed in Europe will be in scope, that is, comparators for non-radiographic axial spondyloarthritis are certolizumab pegol and adalimumab; comparators for ankylosing spondylitis are certolizumab pegol, adalimumab, etanercept, golimumab and infliximab.	The comparators in the scope should reflect the treatments currently used in established clinical practice in England for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Treatments which are used off-label can be considered as comparators if there is evidence to demonstrate that they are routinely used for the indication under appraisal in the NHS. No changes to the scope required.
Population	AbbVie	The ankylosing spondylitis population is accurately described. The Population section mentions that: *"People with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, whose disease has responded inadequately to, or who*	Comment noted. The Committee can only make recommendations on the use of a technology in line with its marketing

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		are intolerant to, NSAIDs." AbbVie thinks that consideration should be given to precisely defining what constitutes objective signs of inflammation, which, for consistency with the licences of drugs currently licensed in the UK for non-radiographic axial SpA, should be elevated CRP and / or positive MRI.	authorisation. The definition of 'objective signs of inflammation', as described in the marketing authorisations for adalimumab and certolizumab pegol has been added to the technology section of the scope for clarity.
	ARUK	We agree that the populations requiring treatment are those outlined in the document.	Comment noted. No changes required.
	British Society for Rheumatology (comment endorsed by the Royal College of Practitioners)	Imaging versus clinical arm fulfilling ASAS criteria.	Comment noted. The Committee will only consider the populations covered by the marketing authorisations for each technology under appraisal.
	National Ankylosing Spondylitis Society (NASS)	*People with severe active ankylosing spondylitis that has responded inadequately to conventional therapy'* This would better be described as: 'People with severe active ankylosing spondylitis whose disease has responded inadequately to, or who are intolerant to, NSAIDs'.	Comment noted. The scope has been amended accordingly.
	Royal College of Nursing	The population is quite clearly defined and assuming that the current criteria for eligibility for anti TNF treatments are kept and added to for the patients without x-ray evidence, this will allow for most patients with severe disease activity to access appropriate treatment.	Comment noted. No changes required.
	UCB	Axial Spondyloarthritis (axSpA) describes a disease spectrum, from non-radiographic axSpA (nr-axSpA) with no definitive evidence for	Comment noted. No

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		sacroiliitis or structural changes in the SI joints on X-ray but typical signs and symptoms of axSpA including evidence for sacroiliitis on MRI, to ankylosing spondylitis (AS) where chronic structural changes in the SI joint are visible on X-ray.	changes required.
Comparators	AbbVie	NSAIDs are standard first line therapy for AS patients in the NHS. The licences for anti-TNF therapies for AS require patients to have had an inadequate response to conventional therapy, therefore all AS patients are expected to have failed or been intolerant to NSAID therapy in the population under consideration. Therefore the appropriate comparators to be considered are other anti-TNF drugs licensed for AS or conventional care (defined as patients remaining on failed NSAIDs despite active disease or, if they are unable to tolerate NSAIDs, palliative care only). For non-radiographic axial Spa, there is no “best alternative care” available in the NHS, as only drugs within the anti-TNFs class are licensed for non-radiographic axial SpA. The standard of care in the NHS for patients covered by the adalimumab and certolizumab licence (who have failed NSAIDs) involves patients maintained on NSAIDs despite active disease, or, if they are unable to tolerate NSAIDs, palliative care only. Physiotherapy is a standard first line adjunct therapy for all patients with axial SpA so is not in itself a comparator. AbbVie also wishes to state that it is worth specifying in the Comparators section of the table which anti-TNFs are currently licensed for the treatment of non-radiographic axial SpA (at the time of writing only adalimumab and certolizumab).	Comment noted. The TNF alfa inhibitors will be compared with each other. At the time of appraisal, the Committee will consider all TNF alfa inhibitors that have a marketing authorisation to treat ankylosing spondylitis or non-radiographic axial spondyloarthritis.
	ARUK	We agree that the comparators are appropriate and the outcomes indicated are those of key importance.	Comment noted. No changes required.
	British Society for Rheumatology (comment	Appropriate.	Comment noted. No changes required.

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	endorsed by the Royal College of Practitioners)		
	Royal College of Nursing	All the anti TNF treatments work effectively with AS and there is no one option that works better, there are preferred options for individuals who also have bowel or eye involvement as options such as Adalimumab are also used to treat these conditions under separate NICE TAGs.	Comment noted. The Committee will consider the clinical effectiveness of all TNF alfa inhibitors included in the scope during the course of the appraisal. No changes required.
	UCB	In line with the ASAS and EULAR recommendations, we understand standard of care (pathway before biologics) to be NSAIDS. We understand that only comparators currently licensed in Europe will be in scope, that is - comparators for non-radiographic axial spondyloarthritis are certolizumab pegol and adalimumab; - comparators for ankylosing spondylitis are certolizumab pegol, adalimumab, etanercept, golimumab and infliximab	Comment noted. The TNF alfa inhibitors will be compared with each other. The comparators in the scope should reflect the treatments currently used in established clinical practice in England for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Treatments which are used off-label can be considered as comparators if there is evidence that they are part of routine practice in the NHS for the condition under appraisal.
Outcomes	AbbVie	Improvements in work productivity for those of working age who are active in the labour force or improvements in ability to carry out normal	Comment noted. Consideration of indirect

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		daily activities for those not active in the labour force are useful outcome measures that should be added. These have been assessed for adalimumab through a variety of instruments such as the Work Productivity and Activity Impairment (WPAI), and for certolizumab using the arthritis-specific Work Productivity Survey (WPS). The outcome measures set specified fails to take into account the relevant outcome measures for Extra-articular Manifestations (EAMs) that are often associated with axial SpA, such as enthesitis, uveitis, inflammatory bowel disease and psoriasis (prevalence of these EAM is discussed in the "Questions for consultation" section). E.g. with respect to psoriasis, clinical outcomes such as skin clearance of plaque and outcomes influencing quality of life such as depression are not considered, and their omission will result in failure to capture the full benefits of anti-TNFs in axial SpA patients.	benefits of treatment (such as work productivity) do not form part of the NICE reference case. However, information about wider societal benefits and costs of treatment can be included in any evidence submission for consideration by the Committee. Peripheral symptoms (such as enthesitis) and Extra-articular manifestations have been included as additional outcome measures in the scope. Please note that the outcomes listed in the scope are not prescriptive or exhaustive. Clinical data for additional outcome measures can be included in the evidence submission from the manufacturer.
	ARUK	Agree [*Will these outcome measures capture the most important health related benefits (and harms) of the technology?]*	Comment noted. No changes required.
	British Society for Rheumatology (comment endorsed by the Royal	Yes [*Will these outcome measures capture the most important health related benefits (and harms) of the technology?]*	Comment noted. No changes required.

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	College of Practitioners)		
	Pfizer	Pfizer request that treatment discontinuation rate is also included.	Comment noted. Treatment discontinuation will be considered as part of 'adverse effects of treatment'. No changes to the scope required.
	Royal College of Nursing	There is a good range of outcome measures listed here and providing they are weighted appropriately should demonstrate the benefits of the treatments. It is important to compare naïve patients with those who are switching as there is more evidence being produced to demonstrate the benefits of using sequential anti TNFs if there is secondary failure, as we now know that the body can develop drug specific antibodies that render the treatment less or ineffective. Also the outcome measure(s) pertaining to work instability (for example work status and productivity), do not appear to have not been included/considered and should be assessed considering the population group being predominately male and of prime working age. An outcome in this domain should include absenteeism and presenteeism.	If evidence allows, the sequential use of treatments will be considered. Please note that the outcomes listed in the scope are not prescriptive or exhaustive. Clinical data for additional outcome measures can be included in the evidence submission from the manufacturer. Consideration of indirect benefits of treatment (such as work productivity) do not form part of the NICE reference case. However, information about wider societal benefits and costs of treatment can be included in any evidence submission for

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			consideration by the Committee.
	UCB	Patient Reported Outcomes (PROs) are critically important to understanding the outcomes of a treatment. Studies utilizing these measures have shown axSpA to have a considerable impact on quality of life. Patients suffer from pain, fatigue, limitations to physical function and disability, as well as experiencing effects on their psychological, social and emotional well-being. Depression and anxiety are common and affect roughly one third of AS patients. Furthermore, impairment due to the disease on workplace activities and within household has also been reported.	Comment noted. Please note that the outcomes listed in the scope are not prescriptive or exhaustive. Clinical data for additional outcome measures can be included in the evidence submission from the manufacturer. No changes to the scope required.
Economic analysis	AbbVie	It would be useful if clarification could be given regarding what resource use items are covered in the Personal Social Services perspective and whether any additional costs of care for SpA patients with high levels of functional impairment beyond those included in the NHS perspective would be included under this perspective.	Comment noted. Manufacturers will be invited to attend a consultee information meeting with NICE and the Assessment Group at the start of the appraisal. Further exploration of any technical issues relating to evidence submissions can be discussed at this meeting.
	British Society for Rheumatology (comment endorsed by the Royal College of Practitioners)	This should include work and work productivity.	Comment noted. Consideration of indirect benefits of treatment (such as work productivity) do not

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			form part of the NICE reference case. However, information about wider societal benefits of treatment can be included in the manufacturer's evidence submission for consideration by the Committee.
	National Ankylosing Spondylitis Society (NASS)	The financial and personal costs of living with AS are substantial. Time away from work, cost of drugs and other treatments, including regular exercise, together with increased insurance premiums, reduced earnings and pension rights renders many people with AS financially disadvantaged compared with their healthy peers. These financial issues are compounded by the personal costs of disease complications, side-effects of both medical and surgical treatment, co-morbidities such as bowel, skin and eye disease and, for those with the most severe forms of AS, a reduced lifespan. The loss of up to one third of people with AS from the workplace has important cost implications both for the individual and society. This is compounded by changes in work patterns and the failure of many individuals with AS to achieve their chosen career or fulfil their potential. Financial costs include the loss of tax revenue from those patients and carers unable to work, and the cost of paying disability living allowance (DLA) and carer's allowance.	Comment noted. Consideration of indirect benefits of treatment (such as work productivity) do not form part of the NICE reference case. However, information about wider societal benefits and costs of treatment can be included in any evidence submission for consideration by the Committee.
	Royal College of Nursing	As this is a long term condition which most commonly presents in the early 20s it is important that the economic analysis takes this into consideration. Short term calculations will not reflect the long term	Comment noted. No changes required.

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		benefits of the treatment in keeping individuals in work and an active member of society.	
	UCB	UCB suggests a lifetime time horizon due to the chronic nature of axSpA and, consequently, the lifelong nature of its treatment and associated costs.	Comment noted. No changes required.
Equality and Diversity	AbbVie	It is understood that AS has a greater prevalence in males than females whereas the prevalence for non-radiographic axial spondyloarthritis is similar for males and females. Given that patients with non-radiographic axial spondyloarthritis have similar levels of pain, disease activity and work and activity impairment compared to AS patients, AbbVie considers that it is important to assess the gender impact of any recommendations made for AS and non-radiographic axial spondyloarthritis.	Comment noted. Any recommendations will be made within the marketing authorisation for the technologies under consideration. The Committee will not discriminate between male and female patients and will ensure that any recommendations do not discriminate against any groups protected under the Equality Act.
	ARUK	The issue of equality of opportunity is relevant to the treatment of women with non-radiographic axial spondyloarthritis (vide supra). Because ankylosing spondylitis (radiographic disease) is more common in men and because the presence of radiographic sacroiliitis has been required for the diagnosis and for the prescribing of TNF inhibitors, this impacts adversely on women with axial spondyloarthritis. It is now clear that many women do not develop radiographic changes or, if they do, are slow to do so. Such women are frequently undiagnosed for long periods and subsequently denied treatment which might well be effective. The inclusion of non-radiographic axial spondyloarthritis	The Committee will ensure that any recommendations do not discriminate against any groups protected under the Equality Act.

Section	Consultees	Comments	Action
		within the NICE guidance would remove this discrepancy. Evidence for the high prevalence of non-radiographic axial spondyloarthritis in women has been provided by cohort studies (4). 4.Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, Braun J, Sieper J. The early disease stage in axial spondylarthritis: Results from the german spondyloarthritis inception cohort. Arthritis & Rheumatism 2009; 60:717–727.	
	National Ankylosing Spondylitis Society (NASS)	Women are less likely than men to develop radiographic changes. Therefore, under current NICE guidance, they are less likely to meet the criteria for anti TNF therapy. If anti TNF therapy could be prescribed for non-radiographic axial spondyloarthritis then women would have more equal access to anti TNF therapy than at present.	Comment noted. This appraisal will consider the use of TNF alfa inhibitors for both ankylosing spondylitis and non-radiographic axial spondyloarthritis. The Committee will ensure that any recommendations do not discriminate against any groups protected under the Equality Act.
	Pfizer	Not to our knowledge.	Comment noted.
	Royal College of Nursing	The current criteria for assessment apply to all individuals with AS and do not appear to disadvantage anyone, the main problem is with individuals who have severe disease who have failed one anti TNF and current NICE guidelines do not allow switching to alternate treatment leaving individuals with severe disease causing disability, affecting college and/or work prospects and impacting on family and social life. We, therefore, believe the inclusion and consideration of all named TNF-alpha inhibitors, in this NICE appraisal, to be relevant and important, as if all are approved (evidence permitting), they will help	Comment noted. All TNF alfa inhibitors licensed to treat ankylosing spondylitis or non-radiographic axial spondyloarthritis at the time of appraisal will be considered by the Committee.

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		promote and significantly improve the treatment options, choices, access of treatments for adults with AS and respective global patient and socioeconomic outcomes. In addition, to help promote equality further. the RCN would welcome NICE's consideration of the All Wales Medicines Strategy Groups recommendation (June 2013) of the use of Adalimumab (Humira®) for the treatment of adults with severe axial spondylitis without radiographic evidence of AS, as currently this treatment option approach only applies to NHS Wales. By agreeing to apply this treatment approach UK wide, this would help reduce the inequality that currently exists. However, with regard the latter indication, Cimzia also has a license for this (but not NICE approval) – therefore, again the RCN would welcome NICE's consideration of this treatment as an additional option for the above, as if it is approved (evidence permitting), this again would help further extend/expand the patient's treatment options, choice and outcomes per se.	
Other considerations	AbbVie	No suggestions.	Comment noted.
	British Society for Rheumatology (comment endorsed by the Royal College of Practitioners)	None.	Comment noted.
	Pfizer	None.	Comment noted.
	Royal College of Nursing	Frequency of clinical review once established on anti-therapy should be considered. Current TAG's suggest three monthly review even though patients show good stable health and improvements after twelve months. Patients find the commitment to attend hospital appointments difficult to accommodate when trying to work as well. The current proposals suggest considering sequential use of TNF	Comment noted. The Committee will be advised during the course of the appraisal on current clinical practice for the management and review of

Section	Consultees	Comments	Action
		treatments which would be very welcome and beneficial to patients. They are also suggesting considering use with non-radiographic AS. This is equally important as it has been known for years that it can take 5-10 years for x-ray changes to become apparent by which time patients may have significant structural change affecting areas such as the spine, pelvis, neck and hips. Potential for switching anti-TNF should be considered if lack of efficacy with 1st line anti-TNF drug. A growing body of evidence suggests support for this. As stated earlier, what is not included in appraisal is information regarding the All Wales Medicines Strategy Group Final Appraisal Recommendation (Advice No:1513 - June 2013) that Adalimumab (Humira®) 40mg prefilled pen or 40mg prefilled syringe is recommended for use within NHS Wales for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAID'S). We would welcome NICE's consideration (evidence permitting) of the sequential use of TNF-alpha inhibitors, as there is some evidence to show that individuals might respond to an alternative anti-TNF because the drugs are slightly structurally different from each other (Lie et al 2011; Glintborg et al 2013) References : • Lie E, van der Heijde D, Uhlig T et al (2011) *Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from NOR-DMARD register*. Annals of the Rheumatic Diseases 70, 1, 157-163	patients in England with ankylosing spondylitis or non-radiographic axial spondyloarthritis. If the evidence allows, sequential use of treatments will be considered.

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		• Glintborg B, Ostergaard M, Krough NS et al (2013) *Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor D inhibitor therapy: results from the Danish nationwide DANBIO registry*. Annals of the Rheumatic Diseases. 72, 7, 1149-1155	
Questions for consultation	AbbVie	Treatment with anti-TNFs for non-radiographic axial SpA patients is innovative and a "step-change" in the management of the condition, as no other drug or class of drugs is currently licensed for the treatment of non-radiographic axial SpA. Patients with non-radiographic axial SpA share a similar burden of disease with patients with AS. For patients with AS the relevant NICE Technology Appraisals ensure equal access to anti-TNFs. For patients with non-radiographic axial SpA patients, due to the absence of NICE guidance, regional differences in access to anti-TNFs potentially exist. As a result, there can be regional variation in access to anti-TNFs for patients with non-radiographic axial SpA when compared to patients with AS. Assessing anti-TNFs for use in non-radiographic axial SpA therefore brings about added benefits in terms of promoting inter-regional equity in England. The QALY calculation is likely to fail to take into account the benefits that treatment with anti-TNFs will provide in reducing the incidence and/or symptoms associated with extra-articular manifestations (EAMs) often associated with axial spondyloarthritis, such as enthesitis, uveitis, inflammatory bowel disease and psoriasis. A significant body of literature supports the prevalence of extra-articular manifestations in axial SpA (see for instance: van der Horst-Bruinsma IE, Nurmohamed MT. Management and evaluation of extra-articular manifestations in spondyloarthritis. Ther Adv Musculoskelet Dis. 2012 Dec; 4(6):413-22. doi: 10.1177/1759720X12458372.)	Comment noted. The innovative nature of all technologies included in the appraisal will be considered by the Committee. Any additional benefits of the technologies which are not adequately captured in the QALY calculation will also be considered.

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		Based primarily on the results of pivotal clinical trials: • Anti-TNFs adalimumab, etanercept and infliximab are licensed in the UK for the treatment of psoriasis and psoriatic arthritis. • Anti-TNFs adalimumab and infliximab are licensed in the UK for the treatment of Crohn's disease and ulcerative colitis. The open-label RHAPSODY study in AS patients treated with adalimumab (Rudwaleit M1, Claudepierre P, Kron M, Kary S, Wong R, Kupper H. Effectiveness of adalimumab in treating patients with ankylosing spondylitis associated with enthesitis and peripheral arthritis. Arthritis Res Ther. 2010; 12(2):R43. doi: 10.1186/ar2953. Epub 2010 Mar 15) showed improved enthesitis, as measured by the change from baseline to week 12 in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES; for patients with MASES of at least 1 at baseline) and the change from baseline to week 12 in the percentage of patients with enthesitis of the plantar fascia (for patients with inflammation of the plantar fascia at baseline). There is also clinical trials evidence supporting the efficacy of adalimumab on the treatment of uveitis. This is summarized in: Rudwaleit M., Rodevand E., Holck P., Vanhoof J., Kron M., Kary S., et al. (2009c) Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. Ann Rheum Dis 68: 696–701. A prospective study by Van-Der Horst-Bruinsma and colleagues (Van Der Horst-Bruinsma I., Van Denderen J., Visman I., Suttorp-Schulten M., Dijkmans B., Nurmohamed M. (2010) Decreased recurrence rate of anterior uveitis in ankylosing spondylitis treated with adalimumab – an interim analysis. Clin Exp Rheumatol 28: 630–630.) showed evidence that patients with AS treated with adalimumab because of high disease activity and screened for uveitis by an ophthalmologist showed a significant decrease (73%) in the recurrence rate of uveitis after one	

Section	Consultees	Comments	Action
		year for patients treated with adalimumab.	
	ARUK	We agree that it is crucial to consider the issues of drug survival and sequential prescribing. It is now clear that secondary failure of TNF inhibitor treatment or drug discontinuation frequently requires an alternative treatment. Presently, only a second or third TNF inhibitor is available to fill that need. Drug survival data from the DANBIO register[5] indicates that drug survival in patients with ankylosing spondylitis is relatively short, though anecdotal experience in the UK is at variance with this. Nonetheless, switching to a second or third TNF inhibitor is commonplace, necessary and may achieve good disease control[6]. Limited data are available to guide prescribers into ensuring maximum benefit from such switch agents though these data are being gathered by the British Society for Rheumatology Biologics Register – AS. 5. Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML.Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis. 2010 Nov;69(11):2002-8. 6. Spadaro A1, Lubrano E, Marchesoni A, D'Angelo S, Ramonda R, Addimanda O, Perrotta FM, Olivieri I, Punzi L, Salvarani C. Remission in ankylosing spondylitis treated with anti-TNF-α drugs: a national multicentre study. Rheumatology (Oxford). 2013 Oct;52(10):1914-9.	Comment noted. Sequential use of TNF alfa inhibitors will be considered if the evidence allows. No changes to the scope required.
	British Society for Rheumatology (comment endorsed by the Royal College of Practitioners)	Yes *[Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?]*	Comment noted. The innovative nature of the technologies will be considered by the Committee during the course of the appraisal. No changes to the scope

Section	Consultees	Comments	Action
			required.
	National Ankylosing Spondylitis Society (NASS)	NASS is aware from our conversations with ankylosing spondylitis patients (3,700+ Helpline calls in 2013), that people with axial spondyloarthritis frequently suffer with the same symptoms (pain, stiffness, fatigue, anxiety etc) as people with ankylosing spondylitis and these symptoms have the same impact on daily living with all the worries for the future that go with that. NASS would like to see anti TNF therapy made available for consultant rheumatologists to prescribe for appropriate axial spondyloarthritis patients. NASS speak to people on the Helpline with axial spondyloarthritis who have failed on all available medications and are really struggling with their symptoms. As an example, we are in contact with a police officer who is suffering a great deal with non-radiographic axial SpA and is really struggling in his work. He worries that he will not be able to continue much longer in the job he loves, has suffered from depression as a likely result of such worries, but his consultant is not able to offer him anti TNF therapy, even though he has failed on a range of other medications. This has left him living in hope of radiographic changes to his sacroiliac joint so that he can start on anti TNF therapy. He would clearly benefit from a trial on anti TNF therapy so he could continue working and supporting his young family. Additionally, in current NICE guidance, ankylosing spondylitis patients can only try one anti TNF. If this does not prove effective, or if the efficacy decreases over time, there is nothing in NICE guidance to allow for a change in therapy, despite the increasing weight of evidence that moving to a second or even a third anti TNF can prove beneficial. If anti TNF therapy fails then patients have effectively reached the end of the line as far as treatment goes.	Comments noted. Sequential use of TNF alfa inhibitors will be considered if the evidence allows. No changes to the scope required.

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		By contrast, in rheumatoid arthritis patients have access to multiple biological therapies including rituximab, abatacept and tocilizumab but these therapies have, so far, not been proven to help in AS. These leaves AS patients disadvantaged in terms of treatment options. This puts an enormous pressure on patients to 'pick the right anti TNF therapy' when they discuss which of the three therapies they would like to try with their nurse. We know that, unless there is a particular clinical reason for patients to have one particular anti TNF therapy they will be offered a choice. Patients can get very stressed and upset when making this choice as they are made aware they don't have the option to change to another anti TNF if this proves to be the wrong choice for them. They currently call the NASS Helpline and join the debate on the forum in an attempt to try and make the right choice. When anti TNF therapy is first discussed, patients do hear stories of the possible 'life-changing' results of such therapies. However, we know that, although around 7 in 10 patients get benefits from anti TNF therapy, 3 in 10 do not find them efficacious. These patients experience a great deal of disappointment and upset when their anti TNF therapy fails, especially if they cannot be offered a second anti TNF. They can be told by their rheumatology department that there is nothing more that can be done for them and are left struggling on NSAIDs and opioids. These are often relatively young people. They may have young families and be working. Anti TNF failure and the inability to try another effective therapy can destroy their lives and lead to psychological problems. Another issue for patients is where the efficacy of anti TNF therapy slowly wears off over time, leaving patients struggling. Currently these patients are unable to try a switch to a different anti TNF to see if this improves efficacy. NASS would strongly advocate that patients should be allowed to switch to/be offered a second anti TNF therapy in these circumstances.	

Section	Consultees	Comments	Action
	Pfizer	Do you consider the technology to be innovative and results in a step change in the management of patients? The treatment currently being evaluated represents both an improvement on existing treatments and a step change in the management of both AS and particularly nr-axSpA. The burden of nr-axSpA is substantial in terms of pain and fatigue, which impacts on physical function, workplace and household productivity, and overall quality of life. The burden of disease is comparable to that of patients with established AS. For patients who can no longer tolerate or have failed to respond to treatment with NSAIDs, TNF- α blockers are recommended in AS. However, there is currently no NICE guidance on biologic treatment in nr-axSpA. Therefore there remains an unmet need for additional treatment options that reduce levels of disease activity, are well tolerated, improve patient quality of life and represent an effective use of healthcare resources/budget. Etanercept brings advanced scientific innovations such as recombinant DNA and cell fusion for the benefit of axial spondyloarthropathy patients. Unlike monoclonal antibodies, the recombinant human TNF receptor fusion protein etanercept, is not associated with neutralising antibodies, and a consequent reduction in efficacy. The production of neutralising antibodies are particularly important in AS and nr-axSpA as methotrexate, which has a potentially immunosuppressant effect (on the production of antibodies), is much less frequently prescribed than in other inflammatory conditions. Having been in the UK market for over a decade, etanercept has demonstrated efficacy, long-term therapeutic benefits as well as good safety and tolerability in the treatment of AS and other arthritis-related disorders. Etanercept trials demonstrate a significant improvement in the management of both AS and nr-axSpA compared with conventional	Comments noted. The innovative nature of the technologies will be considered by the Committee during the course of the appraisal. The Committee will also consider any additional benefits of the technologies which have not been adequately captured in the QALY calculations.

Section	Consultees	Comments	Action
		therapy. The trials show a rapid and sustained clinical response with an established safety profile. This improvement has been demonstrated across a range of indicators that are relevant in clinical practice representing an improvement on standard treatment incorporating without TNF inhibitors. Etanercept has an advantage over intravenously administered TNF inhibitors in that it can be self-administered via a subcutaneous injection and therefore patients have more control over their therapy and can be treated at home. Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Pfizer point out that the following are not captured adequately by the QALY: - Etanercept offers patients relief from a disease that severely impacts on their ability to perform everyday tasks, and self-care. As such etanercept can reduce the burden to care givers. - Axial spondyloarthritis (axSpA) can cause a significant reduction in participation in paid employment and reduced productivity for patients (Boonen et al, 2001). Treatment with etanercept provides the opportunity for patients to return to paid employment. A large UK study by Rafia et al. 2012 showed that "Direct National Health Service funded healthcare costs contributed to just 15% of total costs while unemployment, absenteeism from work and reduced productivity at work accounted for 63.2%, 1.4% and 19.0% of total costs, respectively." - A study examining the impact of AS on employment has shown that over a quarter of patients who were still in paid employment after diagnosis went on to withdraw from paid labour, predominantly for reasons associated with AS (eg physical limitations, fatigue) (Chorus et	

Section	Consultees	Comments	Action
		al, 2002). As the age of onset of symptoms of axSpA is relatively young (ie typically in the third decade of life), there is potential for AS and nr-axSpA to greatly reduce productivity over the course of a patient's life. Have all the relevant comparators been included in the scope? Yes Which treatments are considered to be established clinical practice in the NHS for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis? Established clinical practice within the NHS can include a range of therapies, including NSAIDs, DMARDs, and corticosteroids. Clinical input on the relevance of these therapies to UK clinical practice should be sought during the appraisal.	
	Royal College of Nursing	This appraisal is overdue as there has been increasing evidence that patients have to wait too long for their treatments affecting their physical and psychological wellbeing. In recent years more evidence has been produced to demonstrate that MRIs can show evidence of disease activity much earlier than x-rays. Furthermore evidence is being published on the positive effects of sequential use of anti TNFs. Changes to the availability of these treatments will have a cost implication as more individuals may be eligible for treatment however this needs to be measured against the social and economical costs associated with loss of work, need for carers and benefits over the long term. The Appraisal Committee should have access to all the trial data as well as more current studies. We assume that the assessment group have	Comment noted. The Committee will consider all available evidence on the clinical effectiveness of each technology under appraisal. Sequential use of TNF alfa inhibitors will be considered if the evidence allows. No changes to the scope required.

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		access to all relevant data relating to QALY, although this may not truly and accurately reflect the benefits of these drugs to the individual and society. All these treatments seem to be equally effective in AS and the only concern is the pressure exerted on clinicians to use treatments new to the market over all other options, purely based on cost when there is a lack of longer term safety data. Cost needs to be taken into consideration but individual patients needs may vary depending on comorbidities and not all these treatments treat multiple conditions. Also the earlier comments on Anti-TNFs apply here.	
	UCB	RAPID-axSpA was the first study registration to investigate patients across the active axSpA disease spectrum, including patients both with and without radiographic evidence of sacroiliitis. (Landewé R et al. Efficacy of certolizumab pegol on signs and symptoms of axial Spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2014 Jan 1; 73(1): 39-47). Furthermore, a broad range of outcomes that are clinically meaningful and relevant to patients were evaluated in the RAPID-axSpA study. The study is therefore extremely important as it has demonstrated the efficacy and safety of certolizumab pegol in a patient population with a significant burden of disease but currently very few treatment options.	Comment noted. No changes required.
Additional comments on the draft scope.	AbbVie	No further comments on draft scope.	Comment noted.
	Pfizer	References: Zink A, Braun J, Listing J, et al. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis—results from the German rheumatological database. German Collaborative Arthritis Centers. J Rheumatol 2000 ; 27 : 613 – 22	Comment noted. No changes required.

Section	Consultees	Comments	Action
		van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewé R, Rudwaleit M, Braun J; Assessment of SpondyloArthritis International Society. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis. 2011 Jun; 70(6):905-8. Boonen A, Chorus A, Miedema H, van der Heijde D, van der Tempel H, van der Linden S. Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. Ann Rheum Dis. 2001 Apr; 60(4):353-8. Rafia et al. 2012. Healthcare costs and productivity losses directly attributable to ankylosing spondylitis. Clin Exp Rheumatol. 2012 Mar-Apr; 30(2):246-53. Epub 2012 Apr 13. Chorus AM, Boonen A, Miedema HS, van der Linden S. Employment perspectives of patients with ankylosing spondylitis. Ann Rheum Dis. 2002 Aug; 61(8):693-9.	
	Royal College of Nursing	Also why do AS patients have to wait three months between assessments when for all other conditions it is only a month? The flare patterns are no different and the wait can contribute to the anxiety levels of this group of patients.	Comment noted. The Committee will be advised during the course of the appraisal on current clinical practice for the management and review of patients in England with ankylosing spondylitis or non-radiographic axial spondyloarthritis.

The following consultees/commentators indicated that they had no comments on the draft scope:

Healthcare Improvement Scotland
Department of Health

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (post-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Commissioning Support Appraisals Service (CSAS)	NICE Secretariat		Removed	Following on from the changes within the NHS structure the remit of CSAS has changed. CSAS has been removed from the matrix under 'general commentators'.

2.	Research Institute for the Care of Older People (RICE)	NICE Secretariat		Removed	RICE are mainly interested in research on dementia and Alzheimer's and do not fit the inclusion criteria. They have been removed from the matrix of consultee and comentators under 'research groups'