NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Company comments on the Appraisal Consultation Document from:**
   a. AbbVie
   b. Amgen
   c. Biogen

3. **Consultee and commentator comments on the Appraisal Consultation Document**
   a. National Rheumatoid Arthritis Society
   b. British Society for Rheumatology, *endorsed by the Royal College of Physicians*
   c. British Biosimilars Association

   Comments on the Appraisal Consultation Document from experts
   None received.

4. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Multiple Technology Appraisal

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

Type of stakeholder:

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 Social Care 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 document (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 and Social Care, 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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Commentator	British Biosimilars Association	The British Biosimilars Association (BBA) welcomes the opportunity to comment on NICE's Appraisal Consultation Document (ACD). As a commentator, the Association's feedback is limited to some broad policy observations.	Comment noted.
2	Commentator	British Biosimilars Association	The partial review of TA375 is a significant opportunity to improve access to vital medicines for a larger patient population, particularly as lower cost treatments become available as is the case with biosimilar medicines. However, to allow more patients access to transformative treatments earlier in the pathway, simplicity and speed of process is important. It is therefore critical that NICE plans and prioritises resource accordingly.	Comment noted.
3	Commentator	British Biosimilars Association	In the original Technology Appraisal (2016), the Committee had agreed that biological Disease Modifying Anti-Rheumatic Drugs (DMARDs) should be considered an *"innovative class of drugs"* because they have *"significantly changed the management of rheumatoid arthritis, affecting surgery and hospitalisation."* Furthermore, the Committee accepted that biological DMARDs provide *"extensive benefits for people with rheumatoid arthritis and their families, in terms of both physical and mental health."*	The committee considered the innovative nature of biologics and concluded that the benefits could be captured in the model. See section 3.15 of the FAD.
4	Commentator	British Biosimilars Association	Indeed, in the Association's response to the Assessment Report consultation, we recommended that the Appraisal Committee fully explore the wider societal benefits and improved patient outcomes of earlier patient access as part of the partial review.	Benefits that fall outside of the health service are not part of the reference case outlined in the Guide to the methods of technology appraisal.

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5	Commentator	British Biosimilars Association	However, it is not clear from the ACD whether these factors have been adequately addressed. This is an important consideration which should play a role in the Committee's decision-making on the cost-effective use of NHS resources, particularly if it played a decisive role in the original Technology Appraisal.	See responses to comments 3 and 4.
6	Commentator	British Biosimilars Association	Whilst we recognise the ACD is focused on TA375 specifically, it is the first Technology Appraisal re-review due to biosimilar entry and thus sets an important precedent for future reviews. The below considerations are therefore set against that context but are relevant here.	Comment noted.
7	Commentator	British Biosimilars Association	NICE must ensure that the process for future re-reviews of Technology Appraisals is fundamentally fair to those biosimilar manufacturers who participate in the process.	Comment noted.
8	Commentator	British Biosimilars Association	Any future process should maintain a level playing field and not give competitive advantage to those who do not participate and financially contribute.	Comment noted.
9	Commentator	British Biosimilars Association	We welcome NICE's pragmatic approach to ensure that any future charging mechanism should reflect that similar review processes are also not likely to be full Technology Appraisals and should not be costed as such.	Comment noted.
10	Commentator	British Biosimilars Association	Value for money is an essential consideration for biosimilar manufacturers if their continued participation is to be encouraged.	Comment noted.
11	Commentator	British Biosimilars Association	If the cost of a medicine and a service is taken into account as part of the appraisal, consideration needs to be given to whether the service is used by all eligible patients or only a subset of patients.	Comment noted.
12	Commentator	British	NICE should already be aware of the cost-effectiveness	Comment noted.

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		Biosimilars Association	thresholds that could be triggered as biosimilars enter the market. It should therefore explore an alternative mechanism to accelerate access to biosimilar medicines for more patients in situations where only the price has changed and in consultation with stakeholders.	
13	Commentator	British Biosimilars Association	The British Biosimilars Association (BBA) is the expert sector group of the BGMA exclusively focused on biosimilar medicines. The members of the BBA ensure access to high quality, safe and effective biosimilars for the NHS and patients	Comment noted.
14	Commentator	British Biosimilars Association	Biosimilar medicines are licensed by the medicines regulators (MHRA and EMA) to the same standards of quality, safety and efficacy as the originator product. The increased number of manufacturers helps ensure that the prices of biosimilar medicines are much lower than that of the originator version under patent protection.	Comment noted.
15	Commentator	British Biosimilars Association	Competition from biosimilar medicines also stimulates the research-based pharmaceutical industry to develop new therapies. In keeping medicines affordable for the NHS, this allows further investment in other healthcare priorities, and promotes innovation in the development of new medicines.	Comment noted.
16	Commentator	British Society for Rheumatology	The BSR is grateful for the opportunity to comment on the ACD of the revision of TA375. We have had persistent concern that patients with moderately active RA have been excluded from treatment with advanced therapies for over a decade. We therefore welcome the ACD recommendation 1.1 that adalimumab and infliximab will soon become available for patients with rheumatoid arthritis in moderate disease activity. However, we are also surprised and concerned that the soluble receptor etanercept has not been recommended. We request that the committee reconsider the decision in relation to etanercept. Our reasons are discussed below.	Comment noted.
17	Commentator	British Society for Rheumatology	There are clinical reasons why it is preferable to treat some patients with etanercept rather than one of the monoclonal antibodies, infliximab or adalimumab. Etanercept is a fusion protein of IgG1 Fc with a TNFR2 and not	The committee noted these comments. See section 3.9 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			a monoclonal antibody. One major benefit of etanercept is the considerably reduced risk of reactivating latent tuberculosis with etanercept compared with either of the monoclonal antibodies. Choosing a biologic DAMRD in at risk groups is an important part of management and in populations in England and Wales with high risk of tuberculosis who need a TNF inhibitor, etanercept is the drug of choice. We have discussed this with the National Rheumatoid Arthritis Society and share the opinion that it may be an equality issue to deny access to a safer TNF inhibitor to higher risk populations such as British Asians. We request that the committee approve the use of etanercept for moderate RA especially in those with a risk of latent tuberculosis.	
18	Commentator	British Society for Rheumatology	The ACD does not make any recommendation for those who have an adverse reaction with either infliximab or adalimumab. Adverse effects are relatively common. Some patients have severe injection site reaction. In clinical practice having made a clinical decision to treat with a TNF inhibitor, a patient with a reaction to either the monoclonal antibodies would be switched to etanercept rather than another monoclonal antibody. We urge the committee to approve etanercept in moderate RA and particularly for those who are intolerant of a monoclonal antibody.	Comment noted. The committee has now recommended etanercept.
19	Commentator	British Society for Rheumatology	We previously argued at the TA375 committee meetings in 2015 and subsequent appeal that the ICERs for RA with a DAS>5.1 were similar to those with a DAS from 3.2 to 5.1. However, we noted the comment subsequently made by the Assessment group in discussion (*Stevenson MD et al 2017;44:973-980)* who considered *'Exploratory analyses indicate that if the price of bDMARD (excluding RTX) were reduced by 50%, the mean ICER would decline to £24,500 for patients with severe RA and £31,500 for patients with moderate to severe RA'.* The price of etanercept is now less than 50% of the originator Enbrel. If biosimilar etanercept was available in 2015, the ICER for moderate RA would have been below £30,000/QALY and it would therefore have been approved in TA375 for moderate RA. We fail to	Comment noted. The committee has now recommended etanercept.

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			understand why the Assessment group have changed their opinion but only in relation to etanercept.	
20	Commentator	British Society for Rheumatology	We thank NICE for allowing us to review the revision of the model by the Assessment group prior to the committee meeting. However, we remain concerned that we have been unable to review any of the ICERs for treatment. Modelling in these analyses is an artificial exercise (as evidence by the sequence including tocilizumab which is not approved for moderate RA). Flaws in the model may be apparent if an ICER is generated that is clearly unusually high. We are concerned that the model appears to assume that patients with moderate disease progress to severe disease. This is uncommon. We are also concerned that modelling those with moderate disease who progress to severe disease may dilute the benefit to the remaining cohort. As discussed in our original submission, although many patients with moderate RA may have a flare that increases their DAS>5.1, this does not imply that they progress to severe disease. The majority of patients remain in the moderate DAS category and yet have progressive morbidity.	Comment noted. The precise ICERs can not be shared in order to protect confidential pricing information. In the model only a certain percentage of patients progress from moderate to severe disease.
21	Commentator	British Society for Rheumatology	As we were not able to have sight of the ICERS for etanercept we have difficulty in understanding why it is not within the range accepted by NICE when adalimumab and infliximab are considerably below the threshold. We must assume that the ICER of etanercept cannot be far above the threshold and in view of the uncertainty in analyses, and from the analysis from TA375 in 2016, we request that the committee reconsider their decision and approve etanercept for moderate RA.	The committee has now recommended etanercept.
22	Commentator	National Rheumatoid Arthritis Society	We welcome the ACD recommendation 1.1 that adalimumab and infliximab will be available for patients with rheumatoid arthritis in moderate disease activity. However, we have some comments and seek points of clarification.	Comment noted.
23	Commentator	National Rheumatoid	Although we recognise that the proposed prices of the involved biologics are confidential, the consequential lack of information about individual ICERs	Comment noted. Precise ICERs can not be provided

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		Arthritis Society	renders commentary upon the processes used to derive the recommendations in the NICE ACD unfairly challenging.	in order to protect confidential pricing information.
24	Commentator	National Rheumatoid Arthritis Society	Although we welcome the availability of adalimumab and infliximab for people living with rheumatoid arthritis who are in moderate disease activity, we would ideally also like to have access to etanercept for the treatment of the moderate disease population. The molecular structure of these three biologic anti-TNFs is different; infliximab is a chimaeric monoclonal antibody, adalimumab is a human sequence monoclonal antibody, and etanercept is a fusion protein of IgG1 Fc with a TNFR2. There is heterogeneity of therapeutic response in the case of each of these antibodies and we know that if a subject has an inadequate response or adverse reaction to one, they may respond to another. Furthermore, there are some differences in the risk benefit equation for each. In particular, etanercept has a much lower risk of reactivation of latent TB. This is an equality issue when prescribing anti-TNFs as it may particularly impact certain higher risk populations such as British Asians. We are aware that NICE is very committed to promoting equality of opportunity, and we feel strongly that the preliminary recommendations could have an adverse impact on the above ethnic populations as a consequence of excluding Etanercept.	The committee noted these comments in section 3.9 of the FAD.
25	Commentator	National Rheumatoid Arthritis Society	Throughout the partial review of TA375, NICE have stipulated that “all parameter values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained.” However, as detailed in section 4.8 of the ACD, another sensitivity analysis was done to remove methotrexate after tocilizumab in the treatment sequences following progression to severe disease (in line with NICE’s guidance on filgotinib for treating moderate to severe rheumatoid arthritis). We were told that this “had	The committee considered the sensitivity analysis but retained the assumption used in TA375 in its decision-making.

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			little impact on the ICERs" and, furthermore, that "there was some uncertainty about the efficacy estimates used in the model, which may have influenced the cost-effectiveness results". In light of these issues, we would like to challenge NICE as to whether biosimilar etanercept would have been declared cost-effective if methotrexate had been retained in the comparison sequence in the treatment arm (ie failure of 2 csDMARDs to bDMARD to methotrexate to best supportive care).	
26	Consultee	AbbVie	The Assessment Group (AG) has implemented a significant change to the treatment sequences used in the AG model. Specifically, methotrexate (MTX), which is a proxy for assumed conventional synthetic disease modifying anti-rheumatic drug (csDMARD) efficacy, has been removed from the treatment arm only in moderate disease. This creates an inherent inconsistency between treatment and comparator arms with regards to assumed efficacy of csDMARDs following intensive therapy. This change has a material impact on the incremental cost effectiveness ratio (ICER) calculations for all products under review. We request that this issue is addressed by reverting to the approach consistent with TA375. This would align with the agreed scope of this review and was validated by clinical experts during TA375 as well as 3 other RA appraisals as being the most reflective of clinical practice. For absolute clarity, we have outlined: 1. Approach taken in TA375 and what AbbVie feels would have been a consistent approach with TA375 for this review 2. Why this change is outside the agreed final scope 3. Our contention with NICE's updated approach to modelling moderate RA **<u>1. Approach taken in TA375</u>** The original Assessment Group report from 2013 is clear that "once a patient	The committee considered these comments and agreed that an analysis using the same assumption as TA375 was appropriate for decision making in this appraisal. See section 3.6 of the FAD.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE Response</th></tr>
<tr><td></td><td></td><td></td><td>had received intensive cDMARD therapy and/or the allotted bDMARDs within the sequence, patients were assumed to have one further cDMARD (typically MTX, but an alternative cDMARD if MTX was not suitable) before moving to non-biologic therapy, which was a term defined to encompass a selection of treatments that clinicians may feel was appropriate for individual patients. It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response" (ScHARR Technology Assessment Report 2013, p.347). Importantly, this approach does not stipulate how many or which particular biologic therapies a patient fails before progressing to one final csDMARD (i.e. MTX).

Table 1. Treatment sequences in TA375 (ScHARR Technology Assessment Report 2013, p.348)
<table><tr><td></td><td></td></tr><tr><td>Population 2 and 3</td><td>MTX → non-biologic therapy</td></tr><tr><td></td><td>bDMARD† + MTX → rituximab + MTX→ tocilizumab → MTX → non-biologic therapy</td></tr><tr><td></td><td>tocilizumab → rituximab + MTX → MTX → non-biologic therapy</td></tr></table>cDMARDs = conventional disease-modifying anti-rheumatic drugs; bDMARDs = biological disease-modifying anti-rheumatic drugs; MTX = MTX
Δ excluding abatacept, certolizumab and tocilizumab
† excluding tocilizumab

Since TA375 was published, the appraisals of baricitinib [TA466], tofacitinib [TA480], and sarilumab [TA485] all have progressed to committee recommendations for moderate disease that are consistent with TA375 – i.e. MTX as a proxy for 3rd line csDMARD efficacy applied consistently across both treatment and comparator arms.

In fact, during the clarification stage for TA480 and TA485, the same Evidence Review Group (ScHARR) requested that the companies needed to</td><td></td></tr>
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update the treatment sequences because those in the original company submissions were not consistent with TA375.

Table 2. Final sequences modelled in TA485 to inform decision-making

	Moderate sequences	
	SAR + MTX	**MTX**
1	SAR + MTX	MTX
2	MTX	BSC
3	BSC	
	Severe sequences	
1	TNFi bundle + MTX	
2	RTX + MTX	
3	TCZ IV + MTX	
4	SSZ*	
5	BSC	

BSC, best supportive care; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; SSZ, sulfasalazine; TCZ IV, intravenous tocilizumab; TNFi, tumour necrosis factors inhibitor

*The ERG notes that MTX could replace SSZ in this position

Table 3. Update AbbVie feels would have been a consistent approach with TA375 for this review

	Treatment Arm	Comparator Arm
	Moderate Sequences	
1	bDMARD1	MTX (45.2% efficacy)
2	MTX (45.2% efficacy)	csDMARD (0% efficacy)
3	csDMARD (0% efficacy)	
	Severe Sequences	
1	ADA*	ADA
2	RTX	RTX
3	TCZ	TCZ
4	MTX (45.2% efficacy)	MTX (45.2% efficacy)
5	csDMARD (0% efficacy)	csDMARD (0% efficacy)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			2. Removal of MTX from the treatment arm in moderate disease is beyond the agreed scope for this partial review of TA375 NICE has made clear their intention to conduct a pragmatic review such that "all parameter values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained" (ScHARR Technology Assessment Report 2021, p.24), with only minor updates as per the agreed scope. In this context, a request to update the underlying background mortality data (another parameter within the AG model) was rejected for this review because "to update one parameter without updating the remaining parameters was deemed to deviate from the pragmatic update requested by NICE" (ScHARR Technology Assessment Report 2021, p.9). Similarly, AbbVie take the view that the removal of MTX from the treatment arm only in moderate disease, thereby changing the efficacy assumptions for csDMARDs, is a material deviation from the parameter values preferred by the NICE Appraisal Committee when it produced guidance for TA375. This deviation is contrary to NICE's stated approach and has a material impact on the incremental cost effectiveness ratio (ICER) calculations for all products under review. Therefore, if NICE were to act consistently, this deviation also should be rejected. **3. Our contention with NICE's updated approach to modelling moderate RA** A) In TA375, it was concluded that there was a lack of evidence over the clinical effectiveness of csDMARDs following biologic therapy. As such, MTX	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			was chosen to represent csDMARDs in general and it was assumed to have a EULAR response based on the network meta-analysis (NMA), which was applied consistently at whatever point in the treatment pathway it was positioned and across both the treatment and comparator arms. With no new clinical data and the original NMA, it is unclear on what grounds the Assessment Group feels it is appropriate to change the efficacy assumptions for csDMARDs by removing MTX from the moderate treatment arm only. B) The rationale in section 4.6 of the ACD for including a response to MTX in the moderate comparator arm only, based on it being used as a first treatment, is not factually accurate. This does not account for the fact that patients in both the comparator and treatments arms are assumed to have failed 2 csDMARDs before entering the treatment sequences, even if this is not explicitly modelled. In TA375, the Assessment Group and clinical advisors felt this was representative and so the efficacy assumptions in the AG model for csDMARDs / MTX were applied consistently across both arms, even with intermediate biologic therapy. Without new clinical evidence, the only valid method for this pragmatic review is to retain the approach accepted in TA375.	
27	Consultee	AbbVie	**Transparency and Fairness** AbbVie feels it is necessary to highlight several instances during this review where the level of transparency and fairness has not been maintained to the usual standards expected with NICE processes. This includes: 1. The updated AG report presented to the Appraisal Committee did not make sufficiently clear the removal of MTX in the treatment arm only. 2. It is unclear whether NICE or the Assessment Group sought input	Comment noted. The Assessment Group updated the treatment sequence in response to consultation on the AG report. The aim was to address the issue of the sequence including treatments that are not recommended and/or licensed in moderate RA.

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			from clinical experts prior to changing the efficacy assumptions for csDMARDs in moderate disease. 3. The presentation to the Appraisal Committee, clinical experts, and patient group representatives on 10th March 2021 misinterpreted the treatment sequences and efficacy assumptions in the AG model, giving the impression that they remained consistent with TA375. 4. Following the committee meeting, the Committee slides have been updated. However, the schematic representing the AG model pre-consultation still does not accurately reflect the efficacy assumptions for csDMARDs following failure of the first biologic in moderate disease – as MTX was included in the moderate treatment arm at this stage. It is important for NICE to provide clarity on how the Assessment Group arrived at the decision to remove MTX from the treatment arm only and what steps were taken to validate this fundamental change with clinical experts. In the absence of a robust rationale, the decision to remove MTX from the treatment arm only falls short of the standards of predictability and consistency that NICE aspires to. Additionally, this approach deviates not only from TA375, but also from all guidance for moderate RA published subsequently to TA375 (except TA676). In AbbVie's view the introduction of a significant change in the established approach in moderate RA without clear justification and without validation from clinical experts seriously undermines the fairness of the review process.	The misalignment in assumptions about methotrexate between the updated sequence and TA375 was overlooked. This has now been addressed. See section 3.6 of the FAD.
28	Consultee	Amgen	Amgen support the recommendations made in the Appraisal Consultation Document (ACD) and believe that all evidence has been taken in to account. The summaries of both clinical and cost-effectiveness provide reasonable interpretations of the evidence base.	Comment noted.

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			As outlined in our original submission dossier permitting people with moderate RA (defined as DAS28 score of 3.2 to 5.1) to remain with uncontrolled disease activity is not clinically desirable or appropriate and results in substantial and sustained disability and functional decline, negatively affecting quality of life. A positive recommendation from NICE for adalimumab in moderate RA would be expected to reduce the morbidity and quality of life impairment associated with persistent moderate disease activity, and improve disease management across RA as a whole. Given this we would urge NICE to progress the draft recommendations to Final Guidance and implementation without delay.	
29	Consultee	Biogen	Thank you for the opportunity to comment on the appraisal consultation document (ACD). Following our review, we propose that etanercept should be recommended as an option alongside adalimumab and infliximab for the treatment of adult patients with moderate rheumatoid arthritis (RA). Etanercept's drug characteristics of short half-life, low immunogenicity, and infection risk profile result in its preferential use in the clinical setting for multiple patient groups. The needs of these patient groups are not fully met should etanercept be excluded. When taking consideration of our key comments, etanercept can be recommended as a cost-effective treatment option in patients with moderate RA. The recommendations in the ACD have been restricted beyond the specifications set in the final scope, limiting the patient population that may benefit from the recommendations in this review. As a result, there is a significant unmet need amongst patients with moderate RA; most notably patients who have failed one biologic disease-modifying anti-rheumatic (bDMARD) and remain within the active, moderate RA state (Comment 1). Additionally, a number of patient subgroups require a treatment with a	Comment noted. The committee has now recommended etanercept. Please see responses to individual comments.

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			shorter half-life (Comment 6 and 11).The result of inadequate management of moderate RA can include irreversible disease progression to severe RA, surgical intervention and hospitalisation, and increased pain and anxiety leading to a reduction in patients' quality of life as well as increased cost and NHS resource use.1–3 Moreover, for pregnant women and women planning pregnancy, who in particular may require bDMARD treatment with a short half-life, the lack of suitable treatment options has a disproportionately negative impact on women, raising concerns on equity. Additionally, the innovative status of bDMARDs has not been considered when assessing the cost-effectiveness of the treatments within this partial review, nor have the impacts of the identified uncertainties to cost-effectiveness (Comment 3 and 4). It should be documented how these criteria have been considered when assessing whether the treatments are a cost-effective use of NHS resource, to ensure decision making is fair and transparent. Moreover, drug prices inclusive of homecare are assessed without considering the uptake or comparability of the service offerings or benefits of such services, biasing recommendations towards those companies who do not offer a homecare service or offer a limited service provision (Comment 5). With the proximity of etanercept's incremental cos-effectiveness ratio (ICER) to the £30,000 per quality-adjusted life year (QALY) threshold, we believe these considerations would demonstrate that etanercept is a cost-effective treatment choice for patients with moderate RA. We ask the Committee to consider the comments we raise and revise their recommendations to reflect the patient need, innovative nature of the treatments and range of uncertainty of the ICERs presented by the assessment group, and provide a positive recommendation for the use of etanercept, adalimumab and infliximab for patients with active, moderate RA,	

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			in line with their marketing authorisations.	
30	Consultee	Biogen	The scope of this review has been restricted beyond what was specified in the final scope, limiting the patient population that may benefit from the resulting recommendations The final scope of this review states that treatments should be considered "within their marketing authorisations for treating moderate RA". The marketing authorisation of the treatments under review simply position their use following the failure of conventional disease-modifying anti-rheumatic drugs (cDMARDs) without restriction to use as a first-line bDMARD.[4–7] However, Section 4.2 of the ACD states that "this appraisal only considers first-line biological treatments in moderate disease".[8] Consequently, recommendations are only given for first-line bDMARD use, leaving a gap in recommendations for treating patients who have not adequately responded to a first-line bDMARD until they reach severe RA. Without effective treatments following failure of a first bDMARD in moderate RA, many patients will be left inadequately treated and experience irreversible steps of disease pathogenesis and damage to joints, either progressing to severe RA or remaining within the same health state without remission.[3,9] Patients who do not achieve disease remission face anxiety and stress as their physical pain is compounded by anxiety and frustration that they must wait for their condition to worsen to access effective pharmacological treatments once more; these patients are also likely to suffer a decrease in work productivity, with work impairment experienced by 45% of patients with moderate RA.[10] For patients who never progress to severe disease, the only treatment option may be minor, intermediate or major surgical interventions, which amongst patients with RA, conservatively cost £5,579 on average for each procedure (in 2009) not including hospital stay or rehabilitation costs following surgery.[11] Patients with moderate active RA have an increased risk of	The scope of this review is a pragmatic update of TA375. Only essential updates to the model have been made to ensure robust decision-making. TA375 did not consider modelling beyond first-line use so no revised modelling has been done for this update. Please see section 4.52 of TA375 which notes "The scope for the appraisal includes only the first-line use of biological DMARDs."

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			intermediate and major surgeries compared to those with low disease activity.[3] bDMARDs are associated with a reduction in risk of hospitalisation and surgery; this was identified in TA375 and formed part of the Committee's decision to recognise their innovative nature.[12] Therefore, ensuring effective treatment is received earlier, while patients still have moderate RA, increases the chance of achieving long-term remission; patients are seven times more likely to achieve long-term remission if they achieve early, sustained remission compared to those whose disease activity remains moderate during the first year after diagnosis.[9,13] We ask that the Committee revise their recommendations such that bDMARDs, including adalimumab, infliximab and etanercept, are available to treat patients with moderate, active RA for first- and subsequent-line use, ensuring all relevant patient groups with moderate RA have access to bDMARDs.	
31	Consultee	Biogen	**The cost-effectiveness of tumour necrosis factor (TNF) inhibitors should be considered across a range of positions within the moderate RA treatment pathway, in line with the original review TA375** The cost-effectiveness of TNF inhibitors in moderate RA has only been assessed at one point in the treatment pathway, after two previous monotherapy cDMARDs, and this point in the pathway was not stated in the final scope.[4] The final scope defines the population considered within this review as "adults with moderate, active rheumatoid arthritis, whose disease has responded inadequately to, or who are intolerant of conventional DMARDs";[4] the population is not restricted by the number of previous cDMARDs used. Conversely, the cost-effectiveness of TNF inhibitors in severe RA was assessed at three different points along the treatment pathway in the original review of TA375.[12] There are minor estimated	In TA375 cost-effectiveness in moderate disease was assessed after 2 previous cDMARDs. This is retained for this review.

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			variations in the ICERs of Benepali (etanercept), Imraldi (adalimumab) and Flixabi (infliximab) when used following one previous monotherapy cDMARD or one previous combination cDMARD, compared to following two previous monotherapy cDMARDs currently assessed. As extended use of cDMARDs in patients with moderate RA is associated with low levels of response,[14] ensuring the availability of effective treatments as soon as possible in the treatment pathway can lead to improved clinical outcomes. We ask the Committee to consider the treatments included in this review within the licenced patient population, in line with the marketing authorisation of each treatment, and consider the impact the three different treatment positionings has on the ICER. If treatments are cost-effective across the different positions, they should be available to patients throughout the treatment pathway to ensure that as many patients with moderate RA as possible can benefit from bDMARDs.	
32	Consultee	Biogen	**The innovative nature of etanercept, adalimumab and infliximab has not been considered by the Committee in making the decision to recommend bDMARDs in moderate RA** The NICE Guide to the Methods of Technology Appraisal states in Section 6.3.3 decision making should take account of the "innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" when considering the cost-effectiveness of treatments if the most plausible ICER is above £20,000 per QALY gained.[15] Following the original review of TA375, the Committee "agreed that the biological DMARDs should be considered an innovative class of drugs".[12] With the understanding of the innovative nature of biologics, these treatments were recommended for use in severe, active RA, though the most plausible ICER was above the £20,000-£30,000	The committee considered that all the benefits of biologics could be captured in the model (section 3.15 of the FAD).

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			ICER/QALY threshold that NICE consider a cost-effective use of NHS resources.[12] Indeed, it was stated in the final guidance for TA375 that the most plausible ICER for biologic treatments in severe, active RA lay between £41,600 (the assessment group's base case) and £25,300 (in scenario analyses). In Section 4.14 of the ACD, it is stated that "the committee noted that bDMARDs were considered to be innovative in [TA375] for patients with severe disease".[8] We ask that: 1) The NICE committee explicitly acknowledge the innovative nature of bDMARDs is also relevant to this partial update of TA375 focused on the moderate RA population and update Section 4.14 of the ACD to reflect this. 2) The innovative nature of bDMARDs is considered as a relevant decision-making factor by the NICE committee when assessing the cost-effectiveness and associated uncertainty of such estimates – especially where ICER estimates are close to the threshold. This would allow the recommendations to be extended to include a wider range of treatment options, including etanercept, whose ICER is above the £30,000 cost-effectiveness threshold.	
33	Consultee	Biogen	**Uncertainty remains within the cost-effectiveness estimates, and the impact of this uncertainty has not been fully assessed or acknowledged by the Committee** As stated in Section 4.7 of the ACD, "NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER".8 We have been unable to verify if the uncertainty pertaining to the cost-effectiveness of bDMARDs has been sufficiently	Stakeholders were asked to include in their submission any new evidence which may address the uncertainties in TA375. The assessment group did not consider that anything of relevance had been presented which addressed these

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			considered based on the available information shared with stakeholders to date. During the original review of TA375 numerous sensitivity analyses were performed, including alternative mapping functions and health assessment questionnaire progression relationships. In addition, the direction of impact on the ICER was shared by the committee.[12] In Section 4.8 of the ACD, it states that "several sensitivity analyses" have been conducted, but a comprehensive list of the scenario analyses conducted and their results have not been included in the assessment group report, ACD or slides from the committee meeting.[8] It is important that the committee assess the uncertainty of the cost-effectiveness estimates stemming from the utility mapping function and all other areas of known uncertainty, and the impact that these uncertainties have on the ICERs. These uncertainties were previously identified in TA375, with sizeable impacts to the ICER. For example, use of the Malottki 2011 mapping algorithm and linear health assessment questionnaire progression reduced the assessment group's base case ICER for severe RA to £34,700 and £37,900, respectively, from £41,600.[12] These scenarios are expected to have a similar magnitude of impact on the assessment group's current base case moderate RA ICERs. Additionally, the assessment group's base case results are generated from a discrete event simulation which, due to its probabilistic nature, means that there is some inherent variability in the model outputs. Therefore, results cannot be exactly replicated and their base case ICER has inherent uncertainty that has not been acknowledged or quantified in terms of its proximity to the £30,000 ICER threshold. Moreover, the lack of published ICERs within the ACD, and throughout the review process, obstructs the ability to assess the impact of uncertainty in the cost-effectiveness of	uncertainties. The scenario analyses carried out by the assessment group and considered by the committee are reported in section 3.7 of the FAD. Biogen have been supplied with the assessment group model to assess the inputs and functionality of the cost-effectiveness model. However, exact ICERs can not be provided, to prevent potential disclosure of

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			bDMARDs for moderate RA.8 It should also be stated that withholding ICERs pertaining to Biogen's portfolio is in contradiction with the NICE methods guidance, which stipulates that "data that are likely to be fundamental to the appraisal committee's decision-making cannot be marked as confidential (for example, the list price of a technology after launch and [ICER] estimates)."[16] Moreover, it is not possible to back calculate the discounted prices for each treatment in the model as there is more than one subsequent treatment in the pathway, and so the decision to withhold the ICERs is not justified on the grounds of protecting commercial confidentiality. It is unfair to withhold the base case ICERs, as this impairs the ability of all of the companies participating in the partial review to engage in discussions with NHS England and subsequently patients may be denied access to potentially cost-effective treatments. Considering the described areas of uncertainty, we kindly request that: 1) It is reported whether the upper and lower bounds of the 95% credible intervals for the assessment group's base case ICER of each product are above or below the £30,000 threshold. 2) All scenarios previously assessed for TA375 are evaluated to fully assess the uncertainty associated with the cost-effectiveness of bDMARDs for moderate RA. 3) Stakeholders are provided a full list of all scenario analyses conducted. 4) For each scenario, the committee reports whether this results in an increased or decreased ICER compared to the assessment group's base case, and whether the scenario results in an ICER above or below the £30,000 threshold. 5) The assessment group's base case ICERs for Benepali, Imraldi and Flixabi are confidentially shared with their manufacturer. We believe, using the assessment group's base case, that Benepali is close	confidential pricing information. NICE's policy on handling confidential comparator pricing was agreed with the pharmaceutical industry's representative bodies and has been in place for some time.

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			to the £30,000 per QALY ICER threshold when the price inclusive of homecare [redacted] is considered. Given the proximity of the ICER to the cost-effectiveness threshold, we urge the Committee to consider that the most likely ICER for Benepali is below £30,000 in light of the recognised uncertainty within the model.	
34	Consultee	Biogen	**The drug prices inclusive of homecare have been applied (where available) in the economic analysis to estimate the cost effectiveness, however not all RA patients in the NHS receive products via homecare** The price of treatments inclusive of homecare, where available, have been applied in the cost-effectiveness model. However, currently not all patients receive homecare in the NHS in England. Therefore, using the homecare price only in the model is not reflective of clinical practice and we recommend that the true average cost of bDMARDs to the NHS should be used. Approximately [redacted] of patients receive Benepali via homecare. Using the assessment group's base case, we believe that Benepali is close to the £30,000 per QALY ICER threshold when considering the homecare price, and below £30,000 per QALY when considering the Commercial Medicines Unit submitted price (which excludes homecare). Therefore, it is important the weighted average uptake of homecare products is implemented in the cost-effectiveness model to ensure the ICERs are accurate. Moreover, the equity of the services provided has not been assessed or concluded by the committee. [redacted]	The prices including homecare were used in the modelling because of advice from the commercial medicines unit that most people in the NHS receive products via homecare.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			[redacted] As the recommendations state that treatment should be started 'with the least expensive drug' in Section 1.4 of the ACD, potential bias is introduced in favour of those companies with cheaper homecare, or who do not offer homecare, despite potential disparities between the offerings which have not been quantified. Therefore, the recommendations should facilitate an assessment of the treatment which is most appropriate for the patient. Moreover, if Biogen's homecare support service were to be removed, Benepali may be recommended as a cost-effective treatment as it is believed that the ICER of Benepali at the price agreed with the Commercial Medicines Unit is below £30,000. However, this would have a detrimental impact on the service and support received by patients, negatively impacting clinical outcomes. We request that: 1) Prices reflecting the weighted average uptake of homecare products is implemented in the cost-effectiveness model to ensure ICERs are accurate and reflective of clinical practice in the NHS. 2) The recommendation given in Section 1.4 is revised to include "Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If more than 1 treatment is suitable, start treatment with the least expensive drug…". The recommendations are flexible, and a statement is included in the recommendations to acknowledge that there are differences in homecare offerings with benefits that cannot be monetarily quantified, and these differences should be considered as part of prescribing decisions.	The text in 1.4 has been updated to state "If more than one treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary because of differences in how the drugs are used and treatment schedules." More detail is also provided in section 3.14 of the FAD.
35	Consultee	Biogen	**There will be significant unmet patient need following the**	The committee has now

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			implementation of these draft recommendations As noted in Section 4.1 of the ACD response, "it is important that there is a wide range of treatment options available".[8] Etanercept is the most efficacious treatment option considered within this review, with the highest number of QALYs gained per patient, as reported in Section 6.3 of the assessment group report; under the proposed recommendations, etanercept would not be available until patients reach severe RA, despite evidence for improved clinical outcomes when used in patients with moderate RA.[18,19] Moreover, etanercept is a critical treatment option for patients who require a treatment with a short half-life and may not be recommended to use alternative TNF inhibitors (adalimumab and infliximab); adalimumab and infliximab have half-lives of approximately fourteen days and nine days, respectively, compared to etanercept with a half-life of approximately just three days.[5,6,20] As stated in the clinical guidelines for RA from the South East London Rheumatology Steering Group and BSR biologic DMARD safety guidelines, considerations of patient factors and patient groups who may require treatment with a short half-life include: patients with a history of tuberculosis, where tuberculosis reactivation risk is lower with etanercept compared to other TNF inhibitors; patients at higher risk of infections requiring hospitalisation; patients with co-morbidities or other patient factors such as diabetes, chronic obstructive pulmonary disease or concurrent corticosteroid which may necessitate the use of an alternative treatment to the TNF inhibitors provisionally recommended.[20,21] Etanercept is also a critical treatment option for patients undergoing higher risk surgical procedures who should take their last dose of TNF inhibitor at least 3-5 half-lives prior to surgery.[20] The patient groups identified above are not currently served by the provisional recommendations. Women of childbearing age who may become pregnant in the near future may also require an effective treatment with a short half-life; this is a particularly relevant unmet need as more females are affected by RA than males and this impact on women in	recommended etanercept.

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			particular contradicts the NICE 2010 Equality Act.[22–24] This is discussed in further detail in Comment 11. Additionally, etanercept is an important treatment option for patients who experience an immune response to alternative bDMARDs and so are likely to discontinue treatment; consequently, patients' RA is likely to be sub-optimally managed. As etanercept has lower immunogenicity compared to adalimumab and infliximab, patients have lower risk of antidrug antibodies being induced with etanercept compared to infliximab and adalimumab.[25] Differences in immunogenicity arise from differences in mechanism of action; etanercept competitively inhibits the binding of both TNF and lymphotoxin α to cell surface TNF receptors whereas infliximab and adalimumab bind both cell surface and soluble TNF but not lymphotoxin.[26,27] We ask that the statement in Section 4.2 of the ACD should be revised to reflect that etanercept is a viable alternative treatment option for patients who experience immunogenicity to bDMARD treatment.[8] In light of the above, we ask that the committee: 1) Consider recommending etanercept for patients for whom alternative TNF inhibitors are not suitable, who will not be served by the provisional recommendations. 2) Revise the statement in Section 4.2 of the ACD from "changing the treatment to a drug with a different mechanism of action may be more appropriate if the loss of response is because of the development of antidrug antibodies" to "changing the treatment to a drug, firstly within the TNF inhibitor class then to a different mechanism of action, may be more appropriate if the loss of response is because of the development of antidrug antibodies".	This sentence has been deleted from the guidance.
36	Consultee	Biogen	**The reference to the Commercial Medicines Unit price in the provisional recommendations may be unnecessarily restrictive for**	The assessment of cost-effectiveness is based on

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			hospital trusts Adalimumab and infliximab are both recommended subject to their availability at "the same or lower prices than those agreed with the Commercial Medicines Unit". The price negotiated with the Commercial Medicines Unit is subject to change annually and hospitals may enter into procurement negotiations at a regional trust level price, separate to the Commercial Medicines Unit. Therefore, we request that the committee revise their recommendation to remove the bullet from Section 1.1 in the ACD "the companies provide adalimumab and infliximab at the same or lower prices than those agreed with the Commercial Medicines Unit" to ensure the NHS has flexibility to select the best treatment option from a cost perspective after the guidance is published.[8]	the commercial medicines unit prices. In order to be a cost-effective use of resources, the NHS must pay the same or less than those prices.
37	Consultee	Biogen	**Recommendations are made by molecule which disadvantages companies that paid for participation in this review** As stated in Section 2.1 and 3 of the ACD, not all manufacturers have participated in this partial review.[8] We ask that this be reflected throughout the ACD guidance, as follows: 1) Under Section 2.1, a statement should be added to confirm which manufacturers of which products (including their generic and brand name, and route of administration) have participated in this partial review to reflect their participation in this review. 2) The provisional recommendations that will be carried forward as a result of this review are not limited to the brands that have committed to full participation with this partial review of TA375. We urge the Committee to provide recommendations of the molecules assessed alongside the brand names of products assessed (for example, adalimumab [Imraldi®, pre-filled pen or syringe; and other brands…]),	It is clear in section 2 of the guidance which products/manufacturers have participated in the review.

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			to reflect the full participation offered by these manufacturers and ensure that participation in the review process is not undermined by those who have chosen not to participate.	
38	Consultee	Biogen	**Recommended products have multiple routes of administration that have not all been assessed** The provisional recommendations do not specify the route of administration alongside the molecules recommended in the summary. Infliximab by subcutaneous injection (Remsima) was not considered in this partial review because it was not included in the final scope for TA375, as stated in the footnote of Table 1 of the ACD. We ask that the recommendations are amended to include the route of administration for clarity and to align with the scope of this appraisal.[8]	This information is clear in section 2 of the guidance.
39	Consultee	Biogen	**The proposed date for review of the guidance will not be responsive to fluctuations in price** In the ACD, it is stated that "NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication date of the guidance." However, as the products under review are available through the Commercial Medicines Unit, prices may be adjusted annually. This could result in price-falls that would result in a product in this review to become cost-effective. It would be more appropriate for guidance to be automatically updated in line with specific price fall triggers rather than bound to a 3 year time period. We ask that clarity is provided by NICE and in the ACD on how recommendations will remain aligned with price changes agreed with the Commercial Medicines Unit following the publication of the final guidance, ensuring that if a product is becomes cost-effective after this point, it is available to patients without delay.	All products with commercial medicines unit prices are now recommended.
40	Consultee	Biogen	For both pregnant women and women of childbearing age, half-life and	This is noted in section 3.9

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			thereby biologic washout period is an important consideration in RA treatment selection. When planning pregnancy, women are advised to discontinue treatment with etanercept three weeks prior to stopping contraception, compared to five and six months for adalimumab and infliximab, respectively.[28] If treatment is required during pregnancy due to active disease, etanercept can be used up to the end of the second trimester, due to its shorter half-life and therefore, minimised exposure to the foetus.[29] The absence of a recommendation for a bDMARD with both a short half-life and ability to be used during pregnancy has a disproportionately negative impact on women. The proposed recommendations could leave women that have active disease with limited options following the failure of two cDMARDS in moderate disease; this results in a difficult clinical decision, where the risk of harm to the unborn child has to be considered against the risk of sub-optimally managed RA to the mother. We therefore ask the Committee to consider recommending etanercept as an option for patients with moderate RA, to allow for optimal treatment selection for patients requiring treatment with a shorter half-life compared to infliximab and adalimumab, such as those who wish to conceive or are pregnant.	of the FAD.
41	Web comment (clinical expert 1)	Not specified	Selected text on ACD: **'Adalimumab and infliximab'** *"If only adalimumab, infliximab and filgotinib are approved for moderate disease, this will change treatment pathways with restricted first line bDMARD or tsDMARD options for patients with moderate RA. If based only on cost effectiveness (assuming the same or lower than the agreed CMU acquisition costs) this will not reflect contract changes which may make the other bDMARDs comparatively cost effective, if not cheaper.*	Etanercept is now recommended by the committee.

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			If clinicians favour TNFi 1st line use over JAKi due to clinical experience, with only 2 TNFi available (one for patients who are intolerant of methotrexate) then will we see an increase in cost of these treatments and decreased market competition?" Selected text on ACD: **'Filgotinib is the only advanced treatment option'** *"Making this the only available JAK inhibitor for treating moderate disease will eliminate market competition of other JAK inhibitors."* Selected text on ACD: **'moderate'** *"Just to clarify, I am fully supportive of this for the management of our RA patients, earlier access to effective therapies in the window of opportunity to prevent long term joint damage and disease progression would be another revolution in the treatment of RA, however my concerns are that this has not been appropriately planned.* *- How will secondary care homecare teams absorb this potential influx of work?* *- Will the national capacity of homecare providers cope?* *- How will rheumatology teams cope with the sudden demand on biologics clinics?* *- How will advice line teams / rheumatology pharmacy teams cope with the admin around homecare prescription management and responding to patient queries?* *Treating moderate disease with bDMARD or tsDMARD therapies will have a much greater impact as we will be comparing a cohort of 27.2% of our*	This is not something that can be addressed by the committee in this appraisal. The implementation of NICE guidance will need to be considered by commissioners and providers. Professional organisations and commissioners have been involved in the development of the guidance.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			BNSSG RA patients with severe RA to a cohort of 72.2% of patients who have moderate or severe RA (data for BNSSG CCG region using NICE impact tool for filgotinib)." Selected text on ACD: **'Adalimumab'** *"Moderate RA and methotrexate intolerant means only adalimumab or filgotinib available."* Selected text on ACD: **'Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose).'** *"This is sensible, however you are only permitting cost analysis of adalimumab, infliximab and filgotinib, rather than any of the other therapies. We should be giving clinicians approval to use any of the therapies with comparable efficacy in moderate RA and stipulating that the least expensive drug should be used. We should then be guiding clinicians on how to choose the least expensive drug when clinical and patient parameters have been taken into account. The NHS England best value biologics cost comparator tool will facilitate this with regularly updated CMU contract prices whilst taking into account all additional costs (e.g. administration of IV therapies, homecare fees etc.)."* Selected text on ACD: **'cost-effective use of NHS resources.'** *"In the BNSSG region, we have always used a flexible treatment pathway and cost comparator tool to accommodate changing prices for management*	Etanercept is also recommended by the committee now. The committee has recommended the technologies which are cost-effective for moderate disease.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			of therapies approved for use in severe RA which I feel would be a much more sensible approach for approving therapies to manage moderate disease. *NHS England have agreed to fund setting up a new bDMARD | tsDMARD best value biologic cost comparator tool for our BNSSG region as an internet tool, using the CMU contract prices for the region, which would allow us all to use the more flexible pathway and the regularly updated costs (this is going to be built by RX Info (who built Define / Refine) in the 3rd Q of 2021). The plan is that this could be rolled out nationally after successful implementation and would support clinicians to select the most cost effective therapies (using up to date CMU prices).* *This would be the perfect opportunity to better align NICE's pipeline agenda and CMU's contracting, without needing increased review of NICE TAs."* Selected text on ACD: **'Etanercept'** *"What if an etanercept biosimilar becomes comparable in price to adalimumab or infliximab biosimilar at next contract review (e.g. Aug 2021) and patient has a history of TB (or another clinical parameter dictating that another therapy would be preferable). This TA would be restricting the use of a more appropriate therapy clinically based on potentially outdated cost information, based on snapshot acquisition cost. We need a more timely way of assessing cost which would allow a more generalised NICE TA. The NHSE cost comparator tool would facilitate this."* Selected text on ACD: **'The subcutaneous formulation of Remsima was not considered in this**	Etanercept is now recommended by the committee.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			partial review' *"This immediately makes the review outdated as patients will be told they can't switch to the subcutaneous version, even if cheaper, as wasn't included in the review. Again supporting the notion that we need a more generalised multi TA with more up to date implementation tool to support clinicians with comparing cost of available therapies."* Selected text on ACD: **'This means that it is important for people with rheumatoid arthritis to have a range of different medicines available, even within the same drug class.'** *"However this TA review does the opposite and restricts the treatment options available for moderate RA despite comparable efficacy."* Selected text on ACD: **'It agreed that it was appropriate to assume that after the first biological treatment has failed, NICE technology appraisal guidance for severe rheumatoid arthritis was followed.'** *"Caution - this would potentially be a 'back door' route into accessing all RA therapies for moderate disease. i.e. after failed treatment of a trial of filgotinib, adalimumab or infliximab, a patient with moderate RA can move to the severe RA pathway."* Selected text on ACD: **'But they noted that changing the treatment to a drug with a different mechanism of action may be more appropriate if the loss of response is because of the development of antidrug antibodies.'**	The recommendations for the severe pathway would only apply if the criteria are met i.e. DAS28>5.1. This sentence has been deleted from the guidance.

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			"There is evidence to suggest the contrary, i.e. cycling to an alternative TNFi in the case of secondary failure may be more beneficial than switching class (preferred option in the case of primary failure)." Selected text on ACD: **'The trials in the network meta-analysis included people with moderate and severe disease, so the efficacy of treatments was assumed to be the same in both populations.'** *"This supports the use of the same pathway for both severe and moderate disease with combined use of a cost comparator tool.* *Please feel free to get in touch to discuss the plans for the NHS England best value biologic cost comparator tool and potential use to support the NICE TAs."*	
42	Web comment (clinical expert 2)	East of England Priorities Advisory Committee	***Has all of the relevant evidence been taken into account?*** *"What is the clinical evidence for the impact on the whole of the moderate/severe RA NICE treatment options pathway now that treatment with a biologic and JAK is being offered earlier in the pathway?* *What is the evidence base, economic evaluation and recommendation on the sequential use of adalimumab/ infliximab and filgotinib for moderate disease? This should include JAKi followed by TNFi or TNFi followed by JAKi."* Question 2: **Are the summaries of clinical and cost effectiveness reasonable**	This was not within the scope of this review

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			interpretations of the evidence? *"Clinical evidence:* *The committee agreed "that it was appropriate to assume that after the first biological treatment has failed, NICE technology appraisal guidance for severe rheumatoid arthritis was followed." What consideration has been given to the impact on severe RA guidance when a patient with moderate disease has already failed on a biologic as assumed in Table 2, Treatment sequences used in the updated assessment group model?* *The updated NICE TA375 is recommending that adalimumab/infliximab is offered first line for moderate disease. However, this is also step one used in the model for severe disease considered by the committee. There needs to be an assessment on whether the severe pathway should be amended, and that post 1st line biologic failure for moderate disease, the patient moves on to rituximab as the first treatment for severe disease if the patient has already failed treatment with a biologic/JAK at the moderate disease phase.* *What plans are there to review NICE TA195 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, to consider the impact of the recommendations in NICE TA676 filgotinib and the proposed recommendations in the review of TA375?* *Clarity is needed on how many recommended treatments should be offered to patients with moderate disease. As three drugs, filgotinib, adalimumab and infliximab, will be recommended as cost effective treatments for the same indication, it needs to be clear if there should only be one treatment offered to a patient with moderate disease before they move on to the*	This was not within the scope of this review Only the first-line use of

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			severe pathway, and that patients would revert to conventional DMARDs in the interim. *The body of the text refers to only one bDMARD being used but does not make any reference to using a bDMARD before or after filgotinib as part of the moderate disease pathway. This is unhelpful and further clarity on this point is needed. There are references to filgotinib, but the relative places of the bDMARDs and filgotinib in the treatment of moderate disease is not clear. Table 2 (Treatment sequences used in the updated assessment group model) on page 14 assumes that patients will just revert back to cDMARDs if they don't respond to the first bDMARD.* *Cost effectiveness:* *For each drug you have indicated "The dosage schedule is available in the summary of product characteristics."* *Both adalimumab and infliximab are licensed for dose escalation. Was this considered when calculating the QALY? The guidance needs to be explicit as to what doses of each agent it is recommending as a cost effective treatment, and specifically state that dose escalation is not recommended if this has not been assessed as being cost effective.* *Remsima brand of infliximab was not included in the analysis, therefore the guidance should be clear that it applies to biosimilar IV infliximab only.* *The draft guidance states that "The subcutaneous formulation of Remsima was not considered in this partial review because it was not included in the final scope for NICE technology appraisal 375".* *The guidance needs to specifically state that it is recommending the IV biosimilar formulation of infliximab, and that sub cutaneous infliximab is not recommended as a cost effective treatment option as it has not been*	biologics has been assessed in this review. The cost-effectiveness of dose escalation has not been assessed. Section 1.4 of the recommendations states

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			assessed. Health systems are already under considerable pressure to commission subcut infliximab which is significantly more expensive than etanercept and IV infliximab. *Biosimilar etanercept is only marginally more expensive than biosimilar infliximab IV and it is disappointing that this has not been deemed to be a cost effective treatment as this would have provided an additional option for this group of patients.* *Given that the most cost effective options are now being proposed to be used at the moderate stage of RA, what consideration has been given to the impact this will have on the cost effectiveness of options that have previously been offered for severe disease?"* Question 3: **Are the recommendations sound and a suitable basis for guidance to the NHS?** *"The committee have not made any links between this NICE TA and other related NICE TAs. This not helpful when trying to implement these decisions into practice.* *Clarity is needed around dose escalation, formulations, number of treatment options to be offered as per previous comments. Without this there will be variation in interpretation and implementation at a local level, which will lead to inequalities in patient access to treatments."* Question 4: **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any**	that treatment should start with the least expensive drug. Etanercept is now recommended. This is beyond the scope of this review. Please see responses to previous comments.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? *"Not that we are aware of."* Additional comment: *"The implications of this TA being evaluated in isolation and not in conjunction with other TAs that apply to this patient group e.g. TA676 filgotinib, NICE TA195 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, are problematic.* *The lack of provision of a clear patient pathway or guidance on sequential use of biologics will mean that there is likely to be variation in local interpretation and implementation, which will result in variation in access to treatments for this patient group.* *We would like the committee to note that in our experience, IV infliximab is currently very rarely used to treat RA, so its recommendation for use in moderate disease has the potential to impact on the hospital clinical teams and on day case units, due to increased usage/demand."*	
43	Web comment (clinical expert 3)	Not specified	Question 1: **Has all of the relevant evidence been taken into account?** *"No comment"* Question 2:	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? *"No comment"* Question 3: **Are the recommendations sound and a suitable basis for guidance to the NHS?** *"No comment"* Question 4: **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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** *"I am concerned that Etanercept has been excluded. This is a very good drug for patients with inflammatory arthritis. It does provide an alternative in patients who have side effects to the monoclonal anti TNFs. In addition, Etanercept has a place in those patients who are perhaps prone to infections given it's short half life."*	Etanercept is now recommended
44	Web comment (clinical expert 4)	Not specified	Question 1: **'Has all of the relevant evidence been taken into account?'** *"I welcome the appraisal and the initial document which is a bit step forward for patients and the clinicians looking after them."*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			Question 2: **'Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?'** *"I do have a concern about etanercept not being included-it is not clear to me how regional biosimilar cost differences are incorporated in the cost effectiveness modelling? We may find ourselves in a situation where we use drugs that are more expensive and less clinically desirable . I know rituximab is beyond scope but relevant to the same issue.* *Have the committee considered the dynamic pricing market for biosimilars regionally around the UK and how this affects the cost effectiveness modelling?"*	Etanercept is now recommended.
45	Web comment	NEL Commissioning Support Unit	Question 1: **'Has all of the relevant evidence been taken into account?'** "Yes" *"please see some of our questions below which need to be factored in:* *v Will adalimumab and infliximab be recommended for both moderate and severe RA with this partial review? Currently unclear whether recommendations for these anti-TNFs will supersede previous TA375 and therefore will be only recommended for moderate disease with this update.* *Section 4.2:* *"The clinical experts explained that the cycling of TNF-alpha inhibitors does have a place in treating rheumatoid arthritis. But they noted that changing the treatment to a drug with a different mechanism of action may be more appropriate if the loss of response is because of the development of antidrug*	TA375 recommendations for severe disease continue to stand. The scope of this review is the moderate population only

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			antibodies. They explained that for this reason having a variety of therapeutic choices for moderate disease would benefit people. The committee noted that the scope for the appraisal includes only first-line use of biological DMARDs (after a person's disease has responded inadequately to 2 or more conventional DMARDs) as in NICE technology appraisal 375. It agreed that it was appropriate to assume that after the first biological treatment has failed, NICE technology appraisal guidance for severe rheumatoid arthritis was followed." *v Based on section 4.2, is it correct to assume that sequential use of anti-TNFs for moderate RA is recommended if a person does not tolerate anti-TNF or has no initial response (i.e. primary failure)?* *v Section 4.2 is contradictory (yellow highlighted fields above) and requires clarity. If a person fails either anti-TNF or filgotinib (whichever was started first for moderate RA), clarity is required whether or not one of the other treatments not tried can be used thereafter for moderate disease (if disease is not severe yet) and there was no initial response/loss of response/person did not tolerate first treatment?* *v Clarity is required for why ICER for etanercept has been calculated above £30,000 and consequently not deemed as cost-effective. Noted that infliximab biosimilars are considered cost effective in the guidance and they are more expensive (infliximab administration costs should be taken into consideration if it has not been in this review).* *v Noted only infliximab biosimilars have been considered in this partial review (i.e. neither the originator product nor subcutaneous (SC) product since the manufacturer did not participate for this review). However, clarity is required where a person may start on infliximab biosimilar for moderate disease and then switches under NICE ES29 which allows a switch to its SC formulation for those "with stable disease but who have difficulty attending*	This was not modelled or assessed in this review. Etanercept is now recommended. NICE ES29 is not guidance that is associated with a funding mandate. Technology appraisals do not usually assess

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			hospital appointments?" Question 2: **'Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?'** *"Yes"* Question 3: **'Are the recommendations sound and a suitable basis for guidance to the NHS?'** *"No"* *"Need clarity as per response to the above question."* Question 4: **'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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?'** *"Yes"* *"Yes, pregnancy is not fully covered in the partial review. We understand the manufacturer of certolizumab pegol decided not to participate for this. Both adalimumab and etanercept are compatible in the first and second trimesters of pregnancy whereas certolizumab is compatible with all three trimesters and has reduced placental transfer when compared with other anti-TNF*	reformulations of products. Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			inhibitors. We would like to see the company participate in this review so that pregnant females are not discriminated and given equal options where possible."	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AbbVie
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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1	The Assessment Group (AG) has implemented a significant change to the treatment sequences used in the AG model. Specifically, methotrexate (MTX), which is a proxy for assumed conventional synthetic disease modifying anti-rheumatic drug (csDMARD) efficacy, has been removed from the treatment arm only in moderate disease. This creates an inherent inconsistency between treatment and comparator arms with regards to assumed efficacy of csDMARDs following intensive therapy. This change has a material impact on the incremental cost effectiveness ratio (ICER) calculations for all products under review. We request that this issue is addressed by reverting to the approach consistent with TA375. This would align with the agreed scope of this review and was validated by clinical experts during TA375 as well as 3 other RA appraisals as being the most reflective of clinical practice. For absolute clarity, we have outlined: 1. Approach taken in TA375 and what AbbVie feels would have been a consistent approach with TA375 for this review 2. Why this change is outside the agreed final scope 3. Our contention with NICE's updated approach to modelling moderate RA **1. Approach taken in TA375** The original Assessment Group report from 2013 is clear that "once a patient had received intensive cDMARD therapy and/or the allotted bDMARDs within the sequence, patients were assumed to have one further cDMARD (typically MTX, but an alternative cDMARD if MTX was not suitable) before moving to non-biologic therapy, which was a term defined to encompass a selection of treatments that clinicians may feel was appropriate for individual patients. It was assumed that non-biologic therapy would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response" (ScHARR Technology Assessment Report 2013, p.347). Importantly, this approach does not stipulate how many or which particular biologic therapies a patient fails before progressing to one final csDMARD (i.e. MTX). **Table 1. Treatment sequences in TA375 (ScHARR Technology Assessment Report 2013, p.348)** | | | |---|---| | Population 2 and 3 | MTX → non-biologic therapy | | | bDMARD† + MTX → rituximab + MTX→ tocilizumab → MTX → non-biologic therapy | | | tocilizumab → rituximab + MTX → MTX → non-biologic therapy | cDMARDs = conventional disease-modifying anti-rheumatic drugs; bDMARDs = biological disease-modifying anti-rheumatic drugs; MTX = MTX Δ excluding abatacept, certolizumab and tocilizumab † excluding tocilizumab

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Since TA375 was published, the appraisals of baricitinib [TA466], tofacitinib [TA480], and sarilumab [TA485] all have progressed to committee recommendations for moderate disease that are consistent with TA375 – i.e. MTX as a proxy for 3rd line csDMARD efficacy applied consistently across both treatment and comparator arms.

In fact, during the clarification stage for TA480 and TA485, the same Evidence Review Group (ScHARR) requested that the companies needed to update the treatment sequences because those in the original company submissions were not consistent with TA375.

Table 2. Final sequences modelled in TA485 to inform decision-making

	Moderate sequences	
	SAR + MTX	**MTX**
1	SAR + MTX	MTX
2	MTX	BSC
3	BSC	
	Severe sequences	
1	TNFi bundle + MTX	
2	RTX + MTX	
3	TCZ IV + MTX	
4	SSZ*	
5	BSC	

BSC, best supportive care; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; SSZ, sulfasalazine; TCZ IV, intravenous tocilizumab; TNFi, tumour necrosis factors inhibitor

*The ERG notes that MTX could replace SSZ in this position

Table 3. Update AbbVie feels would have been a consistent approach with TA375 for this review

	Treatment Arm	Comparator Arm
	Moderate Sequences	
1	bDMARD1	MTX (45.2% efficacy)
2	MTX (45.2% efficacy)	csDMARD (0% efficacy)
3	csDMARD (0% efficacy)	
	Severe Sequences	
1	ADA*	ADA
2	RTX	RTX
3	TCZ	TCZ
4	MTX (45.2% efficacy)	MTX (45.2% efficacy)
5	csDMARD (0% efficacy)	csDMARD (0% efficacy)

*INF to be used if ADA is already prescribed in moderate disease

2. Removal of MTX from the treatment arm in moderate disease is beyond the agreed scope for this partial review of TA375

NICE has made clear their intention to conduct a pragmatic review such that “all parameter values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained” (ScHARR Technology Assessment Report 2021, p.24), with only minor updates as per the agreed scope.

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	In this context, a request to update the underlying background mortality data (another parameter within the AG model) was rejected for this review because "to update one parameter without updating the remaining parameters was deemed to deviate from the pragmatic update requested by NICE" (ScHARR Technology Assessment Report 2021, p.9). Similarly, AbbVie take the view that the removal of MTX from the treatment arm only in moderate disease, thereby changing the efficacy assumptions for csDMARDs, is a material deviation from the parameter values preferred by the NICE Appraisal Committee when it produced guidance for TA375. This deviation is contrary to NICE's stated approach and has a material impact on the incremental cost effectiveness ratio (ICER) calculations for all products under review. Therefore, if NICE were to act consistently, this deviation also should be rejected. **3. Our contention with NICE's updated approach to modelling moderate RA** A) In TA375, it was concluded that there was a lack of evidence over the clinical effectiveness of csDMARDs following biologic therapy. As such, MTX was chosen to represent csDMARDs in general and it was assumed to have a EULAR response based on the network meta-analysis (NMA), which was applied consistently at whatever point in the treatment pathway it was positioned and across both the treatment and comparator arms. With no new clinical data and the original NMA, it is unclear on what grounds the Assessment Group feels it is appropriate to change the efficacy assumptions for csDMARDs by removing MTX from the *moderate treatment arm only*. B) The rationale in section 4.6 of the ACD for including a response to MTX in the moderate comparator arm only, based on it being used as a first treatment, is not factually accurate. This does not account for the fact that patients in both the comparator and treatments arms are assumed to have failed 2 csDMARDs before entering the treatment sequences, even if this is not explicitly modelled. In TA375, the Assessment Group and clinical advisors felt this was representative and so the efficacy assumptions in the AG model for csDMARDs / MTX were applied consistently across both arms, even with intermediate biologic therapy. Without new clinical evidence, the only valid method for this pragmatic review is to retain the approach accepted in TA375.
2	**Transparency and Fairness** AbbVie feels it is necessary to highlight several instances during this review where the level of transparency and fairness has not been maintained to the usual standards expected with NICE processes. This includes: 1. The updated AG report presented to the Appraisal Committee did not make sufficiently clear the removal of MTX in the treatment arm only. 2. It is unclear whether NICE or the Assessment Group sought input from clinical experts prior to changing the efficacy assumptions for csDMARDs in moderate disease. 3. The presentation to the Appraisal Committee, clinical experts, and patient group representatives on 10th March 2021 misinterpreted the treatment sequences and efficacy assumptions in the AG model, giving the impression that they remained consistent with TA375.

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	4. Following the committee meeting, the Committee slides have been updated. However, the schematic representing the AG model pre-consultation still does not accurately reflect the efficacy assumptions for csDMARDs following failure of the first biologic in moderate disease – as MTX was included in the moderate treatment arm at this stage. It is important for NICE to provide clarity on how the Assessment Group arrived at the decision to remove MTX from the treatment arm only and what steps were taken to validate this fundamental change with clinical experts. In the absence of a robust rationale, the decision to remove MTX from the treatment arm only falls short of the standards of predictability and consistency that NICE aspires to. Additionally, this approach deviates not only from TA375, but also from all guidance for moderate RA published subsequently to TA375 (except TA676). In AbbVie's view the introduction of a significant change in the established approach in moderate RA without clear justification and without validation from clinical experts seriously undermines the fairness of the review process.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Amgen
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Amgen support the recommendations made in the Appraisal Consultation Document (ACD) and believe that all evidence has been taken in to account. The summaries of both clinical and cost-effectiveness provide reasonable interpretations of the evidence base. As outlined in our original submission dossier permitting people with moderate RA (defined as DAS28 score of 3.2 to 5.1) to remain with uncontrolled disease activity is not clinically desirable or appropriate and results in substantial and sustained disability and functional decline, negatively affecting quality of life. A positive recommendation from NICE for adalimumab in moderate RA would be expected to reduce the morbidity and quality of life impairment associated with persistent moderate disease activity, and improve disease management across RA as a whole. Given this we would urge NICE to progress the draft recommendations to Final Guidance and implementation without delay.
2	
3	
4	
5	
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Biogen Idec Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to disclose.
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive summary	Thank you for the opportunity to comment on the appraisal consultation document (ACD). Following our review, we propose that etanercept should be recommended as an option alongside adalimumab and infliximab for the treatment of adult patients with moderate rheumatoid arthritis (RA). Etanercept's drug characteristics of short half-life, low immunogenicity, and infection risk profile result in its preferential use in the clinical setting for multiple patient groups. The needs of these patient groups are not fully met should etanercept be excluded. When taking consideration of our key comments, etanercept can be recommended as a cost-effective treatment option in patients with moderate RA. The recommendations in the ACD have been restricted beyond the specifications set in the final scope, limiting the patient population that may benefit from the recommendations in this review. As a result, there is a significant unmet need amongst patients with moderate RA; most notably patients who have failed one biologic disease-modifying anti-rheumatic (bDMARD) and remain within the active, moderate RA state (Comment 1). Additionally, a number of patient subgroups require a treatment with a shorter half-life (Comment 6 and 11).The result of inadequate management of moderate RA can include irreversible disease progression to severe RA, surgical intervention and hospitalisation, and increased pain and anxiety leading to a reduction in patients' quality of life as well as increased cost and NHS resource use.[1–3] Moreover, for pregnant women and women planning pregnancy, who in particular may require bDMARD treatment with a short half-life, the lack of suitable treatment options has a disproportionately negative impact on women, raising concerns on equity. Additionally, the innovative status of bDMARDs has not been considered when assessing the cost-effectiveness of the treatments within this partial review, nor have the impacts of the identified uncertainties to cost-effectiveness (Comment 3 and 4). It should be documented how these criteria have been considered when assessing whether the treatments are a cost-effective use of NHS resource, to ensure decision making is fair and transparent. Moreover, drug prices inclusive of homecare are assessed without considering the uptake or comparability of the service offerings or benefits of such services, biasing recommendations towards those companies who do not offer a homecare service or offer a limited service provision (Comment 5). With the proximity of etanercept's incremental cos-

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	effectiveness ratio (ICER) to the £30,000 per quality-adjusted life year (QALY) threshold, we believe these considerations would demonstrate that etanercept is a cost-effective treatment choice for patients with moderate RA. We ask the Committee to consider the comments we raise and revise their recommendations to reflect the patient need, innovative nature of the treatments and range of uncertainty of the ICERs presented by the assessment group, and provide a positive recommendation for the use of etanercept, adalimumab and infliximab for patients with active, moderate RA, in line with their marketing authorisations.
Has all of the relevant evidence been taken into account?	
1	**The scope of this review has been restricted beyond what was specified in the final scope, limiting the patient population that may benefit from the resulting recommendations** The final scope of this review states that treatments should be considered "within their marketing authorisations for treating moderate RA". The marketing authorisation of the treatments under review simply position their use following the failure of conventional disease-modifying anti-rheumatic drugs (cDMARDs) without restriction to use as a first-line bDMARD.[4–7] However, Section 4.2 of the ACD states that "this appraisal only considers first-line biological treatments in moderate disease".[8] Consequently, recommendations are only given for first-line bDMARD use, leaving a gap in recommendations for treating patients who have not adequately responded to a first-line bDMARD until they reach severe RA. Without effective treatments following failure of a first bDMARD in moderate RA, many patients will be left inadequately treated and experience irreversible steps of disease pathogenesis and damage to joints, either progressing to severe RA or remaining within the same health state without remission.[3,9] Patients who do not achieve disease remission face anxiety and stress as their physical pain is compounded by anxiety and frustration that they must wait for their condition to worsen to access effective pharmacological treatments once more; these patients are also likely to suffer a decrease in work productivity, with work impairment experienced by 45% of patients with moderate RA.[10] For patients who never progress to severe disease, the only treatment option may be minor, intermediate or major surgical interventions, which amongst patients with RA, conservatively cost £5,579 on average for each procedure (in 2009) not including hospital stay or rehabilitation costs following surgery.[11] Patients with moderate active RA have an increased risk of intermediate

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	and major surgeries compared to those with low disease activity.[3] bDMARDs are associated with a reduction in risk of hospitalisation and surgery; this was identified in TA375 and formed part of the Committee's decision to recognise their innovative nature.[12] Therefore, ensuring effective treatment is received earlier, while patients still have moderate RA, increases the chance of achieving long-term remission; patients are seven times more likely to achieve long-term remission if they achieve early, sustained remission compared to those whose disease activity remains moderate during the first year after diagnosis.[9,13] We ask that the Committee revise their recommendations such that bDMARDs, including adalimumab, infliximab and etanercept, are available to treat patients with moderate, active RA for first- and subsequent-line use, ensuring all relevant patient groups with moderate RA have access to bDMARDs.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	
2	**The cost-effectiveness of tumour necrosis factor (TNF) inhibitors should be considered across a range of positions within the moderate RA treatment pathway, in line with the original review TA375** The cost-effectiveness of TNF inhibitors in moderate RA has only been assessed at one point in the treatment pathway, after two previous monotherapy cDMARDs, and this point in the pathway was not stated in the final scope.[4] The final scope defines the population considered within this review as "adults with moderate, active rheumatoid arthritis, whose disease has responded inadequately to, or who are intolerant of conventional DMARDs";[4] the population is not restricted by the number of previous cDMARDs used. Conversely, the cost-effectiveness of TNF inhibitors in severe RA was assessed at three different points along the treatment pathway in the original review of TA375.[12] There are minor estimated variations in the ICERs of Benepali (etanercept), Imraldi (adalimumab) and Flixabi (infliximab) when used following one previous monotherapy cDMARD or one previous combination cDMARD, compared to following two previous monotherapy cDMARDs currently assessed. As extended use of cDMARDs in patients with moderate RA is associated with low levels of response,[14] ensuring the availability of effective treatments as soon as possible in the treatment pathway can lead to improved clinical outcomes. We ask the Committee to consider the treatments included in this review within the licenced patient population, in line with the marketing authorisation of each treatment, and consider

	the impact the three different treatment positionings has on the ICER. If treatments are cost-effective across the different positions, they should be available to patients throughout the treatment pathway to ensure that as many patients with moderate RA as possible can benefit from bDMARDs.
3	**The innovative nature of etanercept, adalimumab and infliximab has not been considered by the Committee in making the decision to recommend bDMARDs in moderate RA** The NICE Guide to the Methods of Technology Appraisal states in Section 6.3.3 decision making should take account of the "innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" when considering the cost-effectiveness of treatments if the most plausible ICER is above £20,000 per QALY gained.[15] Following the original review of TA375, the Committee "agreed that the biological DMARDs should be considered an innovative class of drugs".[12] With the understanding of the innovative nature of biologics, these treatments were recommended for use in severe, active RA, though the most plausible ICER was above the £20,000-£30,000 ICER/QALY threshold that NICE consider a cost-effective use of NHS resources.[12] Indeed, it was stated in the final guidance for TA375 that the most plausible ICER for biologic treatments in severe, active RA lay between **£41,600** (the **assessment group's base case**) and £25,300 (in scenario analyses). In Section 4.14 of the ACD, it is stated that "the committee noted that bDMARDs were considered to be innovative in [TA375] for patients with severe disease".[8] We ask that: 1) The NICE committee explicitly acknowledge the innovative nature of bDMARDs is also relevant to this partial update of TA375 focused on the moderate RA population and update Section 4.14 of the ACD to reflect this. 2) The innovative nature of bDMARDs is considered as a relevant decision-making factor by the NICE committee when assessing the cost-effectiveness and associated uncertainty of such estimates – especially where ICER estimates are close to the threshold. This would allow the recommendations to be extended to include a wider range of treatment options, including etanercept, whose ICER is above the £30,000 cost-effectiveness threshold.

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4	**Uncertainty remains within the cost-effectiveness estimates, and the impact of this uncertainty has not been fully assessed or acknowledged by the Committee** As stated in Section 4.7 of the ACD, "NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER".[8] We have been unable to verify if the uncertainty pertaining to the cost-effectiveness of bDMARDs has been sufficiently considered based on the available information shared with stakeholders to date. During the original review of TA375 numerous sensitivity analyses were performed, including alternative mapping functions and health assessment questionnaire progression relationships. In addition, the direction of impact on the ICER was shared by the committee.[12] In Section 4.8 of the ACD, it states that "several sensitivity analyses" have been conducted, but a comprehensive list of the scenario analyses conducted and their results have not been included in the assessment group report, ACD or slides from the committee meeting.[8] It is important that the committee assess the uncertainty of the cost-effectiveness estimates stemming from the utility mapping function and all other areas of known uncertainty, and the impact that these uncertainties have on the ICERs. These uncertainties were previously identified in TA375, with sizeable impacts to the ICER. For example, use of the Malottki 2011 mapping algorithm and linear health assessment questionnaire progression reduced the assessment group's base case ICER for severe RA to £34,700 and £37,900, respectively, from £41,600.[12] These scenarios are expected to have a similar magnitude of impact on the assessment group's current base case moderate RA ICERs. Additionally, the assessment group's base case results are generated from a discrete event simulation which, due to its probabilistic nature, means that there is some inherent variability in the model outputs. Therefore, results cannot be exactly replicated and their base case ICER has inherent uncertainty that has not been acknowledged or quantified in terms of its proximity to the £30,000 ICER threshold. Moreover, the lack of published ICERs within the ACD, and throughout the review process, obstructs the ability to assess the impact of uncertainty in the cost-effectiveness of bDMARDs for moderate RA.[8] It should also be stated that withholding ICERs pertaining to Biogen's portfolio is in contradiction with the NICE methods guidance, which stipulates that "data that are likely to be fundamental to the appraisal committee's decision-making cannot be marked as confidential (for example, the list price of a technology after launch and [ICER] estimates)."[16] Moreover, it is not

	possible to back calculate the discounted prices for each treatment in the model as there is more than one subsequent treatment in the pathway, and so the decision to withhold the ICERs is not justified on the grounds of protecting commercial confidentiality. It is unfair to withhold the base case ICERs, as this impairs the ability of all of the companies participating in the partial review to engage in discussions with NHS England and subsequently patients may be denied access to potentially cost-effective treatments. Considering the described areas of uncertainty, we kindly request that: 1) It is reported whether the upper and lower bounds of the 95% credible intervals for the assessment group's base case ICER of each product are above or below the £30,000 threshold. 2) All scenarios previously assessed for TA375 are evaluated to fully assess the uncertainty associated with the cost-effectiveness of bDMARDs for moderate RA. 3) Stakeholders are provided a full list of all scenario analyses conducted. 4) For each scenario, the committee reports whether this results in an increased or decreased ICER compared to the assessment group's base case, and whether the scenario results in an ICER above or below the £30,000 threshold. 5) The assessment group's base case ICERs for Benepali, Imraldi and Flixabi are confidentially shared with their manufacturer. We believe, using the assessment group's base case, that Benepali is close to the £30,000 per QALY ICER threshold when the price inclusive of homecare [redacted] is considered. Given the proximity of the ICER to the cost-effectiveness threshold, we urge the Committee to consider that the most likely ICER for Benepali is below £30,000 in light of the recognised uncertainty within the model.
5	**The drug prices inclusive of homecare have been applied (where available) in the economic analysis to estimate the cost-effectiveness, however not all RA patients in the NHS receive products via homecare** The price of treatments inclusive of homecare, where available, have been applied in the cost-effectiveness model. However, currently not all patients receive homecare in the NHS in England. Therefore, using the homecare price only in the model is not reflective of clinical

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practice and we recommend that the true average cost of bDMARDs to the NHS should be used. Approximately [redacted] of patients receive Benepali via homecare.

Using the assessment group's base case, we believe that Benepali is close to the £30,000 per QALY ICER threshold when considering the homecare price, and below £30,000 per QALY when considering the Commercial Medicines Unit submitted price (which excludes homecare). Therefore, it is important the weighted average uptake of homecare products is implemented in the cost-effectiveness model to ensure the ICERs are accurate.

Moreover, the equity of the services provided has not been assessed or concluded by the committee. [redacted][17]

As the recommendations state that treatment should be started 'with the least expensive drug' in Section 1.4 of the ACD, potential bias is introduced in favour of those companies with cheaper homecare, or who do not offer homecare, despite potential disparities between the offerings which have not been quantified. Therefore, the recommendations should facilitate an assessment of the treatment which is most appropriate for the patient. Moreover, if Biogen's homecare support service were to be removed, Benepali may be recommended as a cost-effective treatment as it is believed that the ICER of Benepali at the price agreed with the Commercial Medicines Unit is below £30,000. However, this would have a detrimental impact on the service and support received by patients, negatively impacting clinical outcomes.

We request that:

1) Prices reflecting the weighted average uptake of homecare products is implemented in the cost-effectiveness model to ensure ICERs are accurate and reflective of clinical practice in the NHS.

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	2) The recommendation given in Section 1.4 is revised to include "Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If more than 1 treatment is suitable, start treatment with the least expensive drug…". 3) The recommendations are flexible, and a statement is included in the recommendations to acknowledge that there are differences in homecare offerings with benefits that cannot be monetarily quantified, and these differences should be considered as part of prescribing decisions.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	
6	**There will be significant unmet patient need following the implementation of these draft recommendations** As noted in Section 4.1 of the ACD response, "it is important that there is a wide range of treatment options available".[8] Etanercept is the most efficacious treatment option considered within this review, with the highest number of QALYs gained per patient, as reported in Section 6.3 of the assessment group report; under the proposed recommendations, etanercept would not be available until patients reach severe RA, despite evidence for improved clinical outcomes when used in patients with moderate RA.[18,19] Moreover, etanercept is a critical treatment option for patients who require a treatment with a short half-life and may not be recommended to use alternative TNF inhibitors (adalimumab and infliximab); adalimumab and infliximab have half-lives of approximately fourteen days and nine days, respectively, compared to etanercept with a half-life of approximately just three days.[5,6,20] As stated in the clinical guidelines for RA from the South East London Rheumatology Steering Group and BSR biologic DMARD safety guidelines, considerations of patient factors and patient groups who may require treatment with a short half-life include: patients with a history of tuberculosis, where tuberculosis reactivation risk is lower with etanercept compared to other TNF inhibitors; patients at higher risk of infections requiring hospitalisation; patients with co-morbidities or other patient factors such as diabetes, chronic obstructive pulmonary disease or concurrent corticosteroid which may necessitate the use of an alternative treatment to the TNF inhibitors provisionally recommended.[20,21] Etanercept is also a critical treatment option for patients undergoing higher risk surgical procedures who should take their last dose of TNF inhibitor at least 3-5 half-lives prior to surgery.[20] The patient groups identified above are not currently served by the provisional recommendations. Women of childbearing age who may

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	become pregnant in the near future may also require an effective treatment with a short half-life; this is a particularly relevant unmet need as more females are affected by RA than males and this impact on women in particular contradicts the NICE 2010 Equality Act.[22–24] This is discussed in further detail in Comment 11. Additionally, etanercept is an important treatment option for patients who experience an immune response to alternative bDMARDs and so are likely to discontinue treatment; consequently, patients' RA is likely to be sub-optimally managed. As etanercept has lower immunogenicity compared to adalimumab and infliximab, patients have lower risk of antidrug antibodies being induced with etanercept compared to infliximab and adalimumab.[25] Differences in immunogenicity arise from differences in mechanism of action; etanercept competitively inhibits the binding of both TNF and lymphotoxin α to cell surface TNF receptors whereas infliximab and adalimumab bind both cell surface and soluble TNF but not lymphotoxin.[26,27] We ask that the statement in Section 4.2 of the ACD should be revised to reflect that etanercept is a viable alternative treatment option for patients who experience immunogenicity to bDMARD treatment.[8] In light of the above, we ask that the committee: 1) Consider recommending etanercept for patients for whom alternative TNF inhibitors are not suitable, who will not be served by the provisional recommendations. 2) Revise the statement in Section 4.2 of the ACD from "changing the treatment to a drug with a different mechanism of action may be more appropriate if the loss of response is because of the development of antidrug antibodies" to "changing the treatment to a drug, firstly within the TNF inhibitor class then to a different mechanism of action, may be more appropriate if the loss of response is because of the development of antidrug antibodies".
7	**The reference to the Commercial Medicines Unit price in the provisional recommendations may be unnecessarily restrictive for hospital trusts** Adalimumab and infliximab are both recommended subject to their availability at "the same or lower prices than those agreed with the Commercial Medicines Unit". The price negotiated with the Commercial Medicines Unit is subject to change annually and hospitals may enter into procurement negotiations at a regional trust level price, separate to the Commercial Medicines Unit. Therefore, we request that the committee revise their recommendation to remove the bullet from Section 1.1 in the ACD "the companies provide adalimumab and infliximab at the same

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	or lower prices than those agreed with the Commercial Medicines Unit" to ensure the NHS has flexibility to select the best treatment option from a cost perspective after the guidance is published.[8]
8	**Recommendations are made by molecule which disadvantages companies that paid for participation in this review** As stated in Section 2.1 and 3 of the ACD, not all manufacturers have participated in this partial review.[8] We ask that this be reflected throughout the ACD guidance, as follows: 1) Under Section 2.1, a statement should be added to confirm which manufacturers of which products (including their generic and brand name, and route of administration) have participated in this partial review to reflect their participation in this review. 2) The provisional recommendations that will be carried forward as a result of this review are not limited to the brands that have committed to full participation with this partial review of TA375. We urge the Committee to provide recommendations of the molecules assessed alongside the brand names of products assessed (for example, adalimumab [Imraldi®, pre-filled pen or syringe; and other brands…]), to reflect the full participation offered by these manufacturers and ensure that participation in the review process is not undermined by those who have chosen not to participate.
9	**Recommended products have multiple routes of administration that have not all been assessed** The provisional recommendations do not specify the route of administration alongside the molecules recommended in the summary. Infliximab by subcutaneous injection (Remsima) was not considered in this partial review because it was not included in the final scope for TA375, as stated in the footnote of Table 1 of the ACD. We ask that the recommendations are amended to include the route of administration for clarity and to align with the scope of this appraisal.[8]
10	**The proposed date for review of the guidance will not be responsive to fluctuations in price** In the ACD, it is stated that "NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication date of the guidance." However, as the products under review are available through the Commercial

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	Medicines Unit, prices may be adjusted annually. This could result in price-falls that would result in a product in this review to become cost-effective. It would be more appropriate for guidance to be automatically updated in line with specific price fall triggers rather than bound to a 3 year time period. We ask that clarity is provided by NICE and in the ACD on how recommendations will remain aligned with price changes agreed with the Commercial Medicines Unit following the publication of the final guidance, ensuring that if a product is becomes cost-effective after this point, it is available to patients without delay.
Could the preliminary recommendations have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology? **Could the preliminary recommendations have any adverse impact on people with a particular disability or disabilities?**	
11	For both pregnant women and women of childbearing age, half-life and thereby biologic washout period is an important consideration in RA treatment selection. When planning pregnancy, women are advised to discontinue treatment with etanercept three weeks prior to stopping contraception, compared to five and six months for adalimumab and infliximab, respectively.[28] If treatment is required during pregnancy due to active disease, etanercept can be used up to the end of the second trimester, due to its shorter half-life and therefore, minimised exposure to the foetus.[29] The absence of a recommendation for a bDMARD with both a short half-life and ability to be used during pregnancy has a disproportionately negative impact on women. The proposed recommendations could leave women that have active disease with limited options following the failure of two cDMARDS in moderate disease; this results in a difficult clinical decision, where the risk of harm to the unborn child has to be considered against the risk of sub-optimally managed RA to the mother. We therefore ask the Committee to consider recommending etanercept as an option for patients with moderate RA, to allow for optimal treatment selection for patients requiring treatment with a shorter half-life compared to infliximab and adalimumab, such as those who wish to conceive or are pregnant.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	National Rheumatoid Arthritis Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Name of commentator person completing form:	[redacted], NRAS [redacted], NRAS [redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We welcome the ACD recommendation 1.1 that adalimumab and infliximab will be available for patients with rheumatoid arthritis in moderate disease activity. However, we have some comments and seek points of clarification.
2	Although we recognise that the proposed prices of the involved biologics are confidential, the consequential lack of information about individual ICERs renders commentary upon the processes used to derive the recommendations in the NICE ACD unfairly challenging.
3	Although we welcome the availability of adalimumab and infliximab for people living with rheumatoid arthritis who are in moderate disease activity, we would ideally also like to have access to etanercept for the treatment of the moderate disease population. The molecular structure of these three biologic anti-TNFs is different; infliximab is a chimaeric monoclonal antibody, adalimumab is a human sequence monoclonal antibody, and etanercept is a fusion protein of IgG1 Fc with a TNFR2. There is heterogeneity of therapeutic response in the case of each of these antibodies and we know that if a subject has an inadequate response or adverse reaction to one, they may respond to another. Furthermore, there are some differences in the risk benefit equation for each. In particular, etanercept has a much lower risk of reactivation of latent TB. This is an equality issue when prescribing anti-TNFs as it may particularly impact certain higher risk populations such as British Asians. We are aware that NICE is very committed to promoting equality of opportunity, and we feel strongly that the preliminary recommendations could have an adverse impact on the above ethnic populations as a consequence of excluding Etanercept.
4	Throughout the partial review of TA375, NICE have stipulated that “all parameter values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained.” However, as detailed in section 4.8 of the ACD, another sensitivity analysis was done to remove methotrexate after tocilizumab in the treatment sequences following progression to severe disease (in line with NICE’s guidance on filgotinib for treating moderate to severe rheumatoid arthritis). We were told that this “had little impact on the ICERs” and, furthermore, that “there was some uncertainty about the efficacy estimates used in the model, which may have influenced the cost-

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	effectiveness results". In light of these issues, we would like to challenge NICE as to whether biosimilar etanercept would have been declared cost-effective if methotrexate had been retained in the comparison sequence in the treatment arm (ie failure of 2 csDMARDs to bDMARD to methotrexate to best supportive care).
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Society for Rheumatology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The BSR is grateful for the opportunity to comment on the ACD of the revision of TA375. We have had persistent concern that patients with moderately active RA have been excluded from treatment with advanced therapies for over a decade. We therefore welcome the ACD recommendation 1.1 that adalimumab and infliximab will soon become available for patients with rheumatoid arthritis in moderate disease activity. However, we are also surprised and concerned that the soluble receptor etanercept has not been recommended. We request that the committee reconsider the decision in relation to etanercept. Our reasons are discussed below.
2	There are clinical reasons why it is preferable to treat some patients with etanercept rather than one of the monoclonal antibodies, infliximab or adalimumab. Etanercept is a fusion protein of IgG1 Fc with a TNFR2 and not a monoclonal antibody. One major benefit of etanercept is the considerably reduced risk of reactivating latent tuberculosis with etanercept compared with either of the monoclonal antibodies. Choosing a biologic DAMRD in at risk groups is an important part of management and in populations in England and Wales with high risk of tuberculosis who need a TNF inhibitor, etanercept is the drug of choice. We have discussed this with the National Rheumatoid Arthritis Society and share the opinion that it may be an equality issue to deny access to a safer TNF inhibitor to higher risk populations such as British Asians. We request that the committee approve the use of etanercept for moderate RA especially in those with a risk of latent tuberculosis.
3	The ACD does not make any recommendation for those who have an adverse reaction with either infliximab or adalimumab. Adverse effects are relatively common. Some patients have severe injection site reaction. In clinical practice having made a clinical decision to treat with a TNF inhibitor, a patient with a reaction to either the monoclonal antibodies would be switched to etanercept rather than another monoclonal antibody. We urge the committee to approve etanercept in moderate RA and particularly for those who are intolerant of a monoclonal antibody.
4	We previously argued at the TA375 committee meetings in 2015 and subsequent appeal that the ICERs for RA with a DAS>5.1 were similar to those with a DAS from 3.2 to 5.1. However, we noted the comment subsequently made by the Assessment group in discussion (*Stevenson MD et al 2017;44:973-980)* who considered *'Exploratory analyses indicate that if the price of bDMARD (excluding RTX) were reduced by 50%, the mean ICER would decline to £24,500 for patients with severe RA and £31,500 for patients with moderate to severe RA'.* The price of etanercept is

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	now less than 50% of the originator Enbrel. If biosimilar etanercept was available in 2015, the ICER for moderate RA would have been below £30,000/QALY and it would therefore have been approved in TA375 for moderate RA. We fail to understand why the Assessment group have changed their opinion but only in relation to etanercept.
5	We thank NICE for allowing us to review the revision of the model by the Assessment group prior to the committee meeting. However, we remain concerned that we have been unable to review any of the ICERs for treatment. Modelling in these analyses is an artificial exercise (as evidence by the sequence including tocilizumab which is not approved for moderate RA). Flaws in the model may be apparent if an ICER is generated that is clearly unusually high. We are concerned that the model appears to assume that patients with moderate disease progress to severe disease. This is uncommon. We are also concerned that modelling those with moderate disease who progress to severe disease may dilute the benefit to the remaining cohort. As discussed in our original submission, although many patients with moderate RA may have a flare that increases their DAS>5.1, this does not imply that they progress to severe disease. The majority of patients remain in the moderate DAS category and yet have progressive morbidity.
6	As we were not able to have sight of the ICERS for etanercept we have difficulty in understanding why it is not within the range accepted by NICE when adalimumab and infliximab are considerably below the threshold. We must assume that the ICER of etanercept cannot be far above the threshold and in view of the uncertainty in analyses, and from the analysis from TA375 in 2016, we request that the committee reconsider their decision and approve etanercept for moderate RA.

Insert extra rows as needed

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attachments, it must send it by the deadline.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Biosimilars Association**
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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The British Biosimilars Association (BBA) welcomes the opportunity to comment on NICE's Appraisal Consultation Document (ACD). As a commentator, the Association's feedback is limited to some broad policy observations.
2	The partial review of TA375 is a significant opportunity to improve access to vital medicines for a larger patient population, particularly as lower cost treatments become available as is the case with biosimilar medicines. However, to allow more patients access to transformative treatments earlier in the pathway, simplicity and speed of process is important. It is therefore critical that NICE plans and prioritises resource accordingly.
3	In the original Technology Appraisal (2016), the Committee had agreed that biological Disease Modifying Anti-Rheumatic Drugs (DMARDs) should be considered an *"innovative class of drugs"* because they have *"significantly changed the management of rheumatoid arthritis, affecting surgery and hospitalisation."* Furthermore, the Committee accepted that biological DMARDs provide *"extensive benefits for people with rheumatoid arthritis and their families, in terms of both physical and mental health."*
4	Indeed, in the Association's response to the Assessment Report consultation, we recommended that the Appraisal Committee fully explore the wider societal benefits and improved patient outcomes of earlier patient access as part of the partial review.
5	However, it is not clear from the ACD whether these factors have been adequately addressed. This is an important consideration which should play a role in the Committee's decision-making on the cost-effective use of NHS resources, particularly if it played a decisive role in the original Technology Appraisal.
6	Whilst we recognise the ACD is focused on TA375 specifically, it is the first Technology Appraisal re-review due to biosimilar entry and thus sets an important precedent for future reviews. The below considerations are therefore set against that context but are relevant here.
7	NICE must ensure that the process for future re-reviews of Technology Appraisals is fundamentally fair to those biosimilar manufacturers who participate in the process.
8	Any future process should maintain a level playing field and not give competitive advantage to those who do not participate and financially contribute.
9	We welcome NICE's pragmatic approach to ensure that any future charging mechanism should reflect that similar review processes are also not likely to be full Technology Appraisals and should not be costed as such.
10	Value for money is an essential consideration for biosimilar manufacturers if their continued participation is to be encouraged.
11	If the cost of a medicine and a service is taken into account as part of the appraisal, consideration needs to be given to whether the service is used by all eligible patients or only a subset of patients.
12	NICE should already be aware of the cost-effectiveness thresholds that could be triggered as biosimilars enter the market. It should therefore explore an alternative mechanism to accelerate access to biosimilar medicines for more patients in situations where only the price has changed and in consultation with stakeholders.
13	The British Biosimilars Association (BBA) is the expert sector group of the BGMA exclusively focused

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	on biosimilar medicines. The members of the BBA ensure access to high quality, safe and effective biosimilars for the NHS and patients
14	Biosimilar medicines are licensed by the medicines regulators (MHRA and EMA) to the same standards of quality, safety and efficacy as the originator product. The increased number of manufacturers helps ensure that the prices of biosimilar medicines are much lower than that of the originator version under patent protection.
15	Competition from biosimilar medicines also stimulates the research-based pharmaceutical industry to develop new therapies. In keeping medicines affordable for the NHS, this allows further investment in other healthcare priorities, and promotes innovation in the development of new medicines.

Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Organisation	Not specified
Conflict	N/A
Comments on the ACD:	

Selected text on ACD:
'Adalimumab and infliximab'

"If only adalimumab, infliximab and filgotinib are approved for moderate disease, this will change treatment pathways with restricted first line bDMARD or tsDMARD options for patients with moderate RA. If based only on cost effectiveness (assuming the same or lower than the agreed CMU acquisition costs) this will not reflect contract changes which may make the other bDMARDs comparatively cost effective, if not cheaper.

If clinicians favour TNFi 1st line use over JAKi due to clinical experience, with only 2 TNFi available (one for patients who are intolerant of methotrexate) then will we see an increase in cost of these treatments and decreased market competition?"

Selected text on ACD:
'Filgotinib is the only advanced treatment option'

"Making this the only available JAK inhibitor for treating moderate disease will eliminate market competition of other JAK inhibitors."

Selected text on ACD:
'moderate'

"Just to clarify, I am fully supportive of this for the management of our RA patients, earlier access to effective therapies in the window of opportunity to prevent long term joint damage and disease progression would be another revolution in the treatment of RA, however my concerns are that this has not been appropriately planned.

- *How will secondary care homecare teams absorb this potential influx of work?*
- *Will the national capacity of homecare providers cope?*
- *How will rheumatology teams cope with the sudden demand on biologics clinics?*
- *How will advice line teams / rheumatology pharmacy teams cope with the admin around homecare prescription management and responding to patient queries?*

Treating moderate disease with bDMARD or tsDMARD therapies will have a much greater impact as we will be comparing a cohort of 27.2% of our BNSSG RA patients with severe RA to a cohort of 72.2% of patients who have moderate or severe RA (data for BNSSG CCG region using NICE impact tool for filgotinib)."

Selected text on ACD:
'Adalimumab'

“Moderate RA and methotrexate intolerant means only adalimumab or filgotinib available.”

Selected text on ACD:
‘Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose).’

“This is sensible, however you are only permitting cost analysis of adalimumab, infliximab and filgotinib, rather than any of the other therapies. We should be giving clinicians approval to use any of the therapies with comparable efficacy in moderate RA and stipulating that the least expensive drug should be used. We should then be guiding clinicians on how to choose the least expensive drug when clinical and patient parameters have been taken into account. The NHS England best value biologics cost comparator tool will facilitate this with regularly updated CMU contract prices whilst taking into account all additional costs (e.g. administration of IV therapies, homecare fees etc.).”

Selected text on ACD:
‘cost-effective use of NHS resources.’

"In the BNSSG region, we have always used a flexible treatment pathway and cost comparator tool to accommodate changing prices for management of therapies approved for use in severe RA which I feel would be a much more sensible approach for approving therapies to manage moderate disease.

NHS England have agreed to fund setting up a new bDMARD | tsDMARD best value biologic cost comparator tool for our BNSSG region as an internet tool, using the CMU contract prices for the region, which would allow us all to use the more flexible pathway and the regularly updated costs (this is going to be built by RX Info (who built Define / Refine) in the 3rd Q of 2021). The plan is that this could be rolled out nationally after successful implementation and would support clinicians to select the most cost effective therapies (using up to date CMU prices).

This would be the perfect opportunity to better align NICE's pipeline agenda and CMU's contracting, without needing increased review of NICE TAs."

Selected text on ACD:
‘Etanercept’

“What if an etanercept biosimilar becomes comparable in price to adalimumab or infliximab biosimilar at next contract review (e.g. Aug 2021) and patient has a history of TB (or another clinical parameter dictating that another therapy would be preferable). This TA would be restricting the use of a more appropriate therapy clinically based on potentially outdated cost information, based on snapshot acquisition cost. We need a more timely way of assessing cost which would allow a more generalised NICE TA. The NHSE cost comparator tool would facilitate this.”

Selected text on ACD:
‘The subcutaneous formulation of Remsima was not considered in this partial review’

“This immediately makes the review outdated as patients will be told they can't switch to the subcutaneous version, even if cheaper, as wasn't included in the review. Again supporting the notion that we need a more generalised multi TA with

more up to date implementation tool to support clinicians with comparing cost of available therapies."

Selected text on ACD:
'This means that it is important for people with rheumatoid arthritis to have a range of different medicines available, even within the same drug class.'

"However this TA review does the opposite and restricts the treatment options available for moderate RA despite comparable efficacy."

Selected text on ACD:
'It agreed that it was appropriate to assume that after the first biological treatment has failed, NICE technology appraisal guidance for severe rheumatoid arthritis was followed.'

"Caution - this would potentially be a 'back door' route into accessing all RA therapies for moderate disease. i.e. after failed treatment of a trial of filgotinib, adalimumab or infliximab, a patient with moderate RA can move to the severe RA pathway."

Selected text on ACD:
'But they noted that changing the treatment to a drug with a different mechanism of action may be more appropriate if the loss of response is because of the development of antidrug antibodies.'

"There is evidence to suggest the contrary, i.e. cycling to an alternative TNFi in the case of secondary failure may be more beneficial than switching class (preferred option in the case of primary failure)."

Selected text on ACD:
'The trials in the network meta-analysis included people with moderate and severe disease, so the efficacy of treatments was assumed to be the same in both populations.'

"This supports the use of the same pathway for both severe and moderate disease with combined use of a cost comparator tool.

Please feel free to get in touch to discuss the plans for the NHS England best value biologic cost comparator tool and potential use to support the NICE TAs."

Name	[redacted]
Role	Not specified
Organisation	East of England Priorities Advisory Committee
Conflict	N/A
Comments on the ACD:	

Question 1:
Has all of the relevant evidence been taken into account?

"What is the clinical evidence for the impact on the whole of the moderate/severe RA NICE treatment options pathway now that treatment with a biologic and JAK is being offered earlier in the pathway?

What is the evidence base, economic evaluation and recommendation on the sequential use of adalimumab/ infliximab and filgotinib for moderate disease? This should include JAKi followed by TNFi or TNFi followed by JAKi."

Question 2:
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"Clinical evidence:

The committee agreed "that it was appropriate to assume that after the first biological treatment has failed, NICE technology appraisal guidance for severe rheumatoid arthritis was followed." What consideration has been given to the impact on severe RA guidance when a patient with moderate disease has already failed on a biologic as assumed in Table 2, Treatment sequences used in the updated assessment group model?

The updated NICE TA375 is recommending that adalimumab/infliximab is offered first line for moderate disease. However, this is also step one used in the model for severe disease considered by the committee. There needs to be an assessment on whether the severe pathway should be amended, and that post 1st line biologic failure for moderate disease, the patient moves on to rituximab as the first treatment for severe disease if the patient has already failed treatment with a biologic/JAK at the moderate disease phase.

What plans are there to review NICE TA195 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, to consider the impact of the recommendations in NICE TA676 filgotinib and the proposed recommendations in the review of TA375?

Clarity is needed on how many recommended treatments should be offered to patients with moderate disease. As three drugs, filgotinib, adalimumab and infliximab, will be recommended as cost effective treatments for the same indication, it needs to be clear if there should only be one treatment offered to a patient with moderate disease before they move on to the severe pathway, and that patients would revert to conventional DMARDs in the interim.

The body of the text refers to only one bDMARD being used but does not make any reference to using a bDMARD before or after filgotinib as part of the moderate disease pathway. This is unhelpful and further clarity on this point is needed. There are references to filgotinib, but the relative places of the bDMARDs and filgotinib in the treatment of moderate disease is not clear. Table 2 (Treatment sequences used in the updated assessment group model) on page 14 assumes that patients will just revert back to cDMARDs if they don't respond to the first bDMARD.

Cost effectiveness:

For each drug you have indicated "The dosage schedule is available in the summary of product characteristics."
Both adalimumab and infliximab are licensed for dose escalation. Was this considered when calculating the QALY? The guidance needs to be explicit as to what doses of each agent it is recommending as a cost effective treatment, and specifically state that dose escalation is not recommended if this has not been assessed as being cost effective.

Remsima brand of infliximab was not included in the analysis, therefore the guidance should be clear that it applies to biosimilar IV infliximab only.

The draft guidance states that "The subcutaneous formulation of Remsima was not considered in this partial review because it was not included in the final scope for NICE technology appraisal 375".
The guidance needs to specifically state that it is recommending the IV biosimilar formulation of infliximab, and that sub cutaneous infliximab is not recommended as a cost effective treatment option as it has not been assessed. Health systems are already under considerable pressure to commission subcut infliximab which is significantly more expensive than etanercept and IV infliximab.

Biosimilar etanercept is only marginally more expensive than biosimilar infliximab IV and it is disappointing that this has not been deemed to be a cost effective treatment as this would have provided an additional option for this group of patients.

Given that the most cost effective options are now being proposed to be used at the moderate stage of RA, what consideration has been given to the impact this will have on the cost effectiveness of options that have previously been offered for severe disease?"

Question 3:
Are the recommendations sound and a suitable basis for guidance to the NHS?

"The committee have not made any links between this NICE TA and other related NICE TAs. This not helpful when trying to implement these decisions into practice.

Clarity is needed around dose escalation, formulations, number of treatment options to be offered as per previous comments. Without this there will be variation in interpretation and implementation at a local level, which will lead to inequalities in patient access to treatments."

Question 4:
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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"Not that we are aware of."

Additional comment:

"The implications of this TA being evaluated in isolation and not in conjunction with other TAs that apply to this patient group e.g. TA676 filgotinib, NICE TA195 Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, are problematic.

The lack of provision of a clear patient pathway or guidance on sequential use of biologics will mean that there is likely to be variation in local interpretation and implementation, which will result in variation in access to treatments for this patient group.

We would like the committee to note that in our experience, IV infliximab is currently very rarely used to treat RA, so its recommendation for use in moderate disease has the potential to impact on the hospital clinical teams and on day case units, due to increased usage/demand."

Name	[redacted]
Role	Not specified
Organisation	Not specified
Conflict	N/A
Comments on the ACD:	

Question 1:
Has all of the relevant evidence been taken into account?

"No comment"

Question 2:
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"No comment"

Question 3:
Are the recommendations sound and a suitable basis for guidance to the NHS?

"No comment"

Question 4:
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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"I am concerned that Etanercept has been excluded. This is a very good drug for patients with inflammatory arthritis. It does provide an alternative in patients who have side effects to the monoclonal anti TNFs. In addition, Etanercept has a place in those patients who are perhaps prone to infections given it's short half life."

Name	[redacted]
Role	Not specified
Organisation	Not specified
Conflict	N/A
Comments on the ACD:	

Question 1:
'Has all of the relevant evidence been taken into account?'

"I welcome the appraisal and the initial document which is a bit step forward for patients and the clinicians looking after them."

Question 2:
'Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?'

"I do have a concern about etanercept not being included-it is not clear to me how regional biosimilar cost differences are incorporated in the cost effectiveness modelling? We may find ourselves in a situation where we use drugs that are more expensive and less clinically desirable . I know rituximab is beyond scope but relevant to the same issue.

Have the committee considered the dynamic pricing market for biosimilars regionally around the UK and how this affects the cost effectiveness modelling?"

Name	[redacted]
Role	Not specified
Organisation	NEL Commissioning Support Unit
Conflict	N/A

Comments on the ACD:

Question 1:
'Has all of the relevant evidence been taken into account?'

"Yes"

"please see some of our questions below which need to be factored in:

v Will adalimumab and infliximab be recommended for both moderate and severe RA with this partial review? Currently unclear whether recommendations for these anti-TNFs will supersede previous TA375 and therefore will be only recommended for moderate disease with this update.

Section 4.2:
"The clinical experts explained that the cycling of TNF-alpha inhibitors does have a place in treating rheumatoid arthritis. But they noted that changing the treatment to a drug with a different mechanism of action may be more appropriate if the loss of response is because of the development of antidrug antibodies. They explained that for this reason having a variety of therapeutic choices for moderate disease would benefit people. The committee noted that the scope for the appraisal includes only first-line use of biological DMARDs (after a person's disease has responded inadequately to 2 or more conventional DMARDs) as in NICE technology appraisal 375. It agreed that it was appropriate to assume that after the first biological treatment has failed, NICE technology appraisal guidance for severe rheumatoid arthritis was followed."

v Based on section 4.2, is it correct to assume that sequential use of anti-TNFs for moderate RA is recommended if a person does not tolerate anti-TNF or has no initial response (i.e. primary failure)?
v Section 4.2 is contradictory (yellow highlighted fields above) and requires clarity. If a person fails either anti-TNF or filgotinib (whichever was started first for moderate RA), clarity is required whether or not one of the other treatments not tried can be used thereafter for moderate disease (if disease is not severe yet) and there was no initial response/loss of response/person did not tolerate first treatment?

v Clarity is required for why ICER for etanercept has been calculated above £30,000 and consequently not deemed as cost-effective. Noted that infliximab biosimilars are considered cost effective in the guidance and they are more expensive (infliximab administration costs should be taken into consideration if it

has not been in this review).
v Noted only infliximab biosimilars have been considered in this partial review (i.e. neither the originator product nor subcutaneous (SC) product since the manufacturer did not participate for this review). However, clarity is required where a person may start on infliximab biosimilar for moderate disease and then switches under NICE ES29 which allows a switch to its SC formulation for those "with stable disease but who have difficulty attending hospital appointments?"

Question 2:
'Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?'

"Yes"

Question 3:
'Are the recommendations sound and a suitable basis for guidance to the NHS?'

"No"

"Need clarity as per response to the above question."

Question 4:
'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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?'

"Yes"

"Yes, pregnancy is not fully covered in the partial review. We understand the manufacturer of certolizumab pegol decided not to participate for this. Both adalimumab and etanercept are compatible in the first and second trimesters of pregnancy whereas certolizumab is compatible with all three trimesters and has reduced placental transfer when compared with other anti-TNF inhibitors. We would like to see the company participate in this review so that pregnant females are not discriminated and given equal options where possible."