NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Appraisal title: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

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

Definitions:

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

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

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

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

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

Comments received from consultees

Consultee	Comment	Response
British Society for Rheumatology	We thank the Appraisal Committee for the opportunity to comment on the recent appraisal consultation document issued June 2015. Our comments are focussed on three main areas: 1. On-going access to bDMARDs in patients with severe, active rheumatoid arthritis 2. Removal of access to bDMARDs for patients with intolerance and/or contra-indications to methotrexate 3. Lack of access to bDMARDs in patients with moderate disease **Access to bDMARDs in severe, active rheumatoid arthritis.** We are pleased that NICE have recognised the value that bDMARDs add to the care of patients with active, severe rheumatoid arthritis and are relieved that NHS patients will continue to have access to these life-changing therapies. We accept that only patients at highest risk of progressive joint damage should receive these therapies, and agree that active synovitis despite combination cDMARD therapy is a clinically useful indicator of poor outcome for those with severe disease. This represents a stricter eligibility threshold than previous MTAs but is in line with the modern treatment of rheumatoid arthritis and national (NICE, BSR) and international (EULAR) guidelines.	Thank you for your comment. Comment noted, no actions required.
British Society for Rheumatology	**Removal of access to bDMARDs for patients with intolerance and/or contra-indications to methotrexate** We are concerned that the committee '*was not persuaded that biological DMARDs were a cost-effective use of NHS resources when used as monotherapy'*. The removal of access to bDMARDs for patients who cannot take methotrexate is disappointing and represents a significant change to routine clinical practice, contradicting previous NICE technology appraisals (TA 130, TA186, TA195, TA247) and introducing significant variation from current	Comment noted. The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from

	NICE guidance on the management of RA (CG79). Observational national registry data (both UK and elsewhere) suggest that a number of patients are unable to take methotrexate and receive bDMARDs as monotherapy. This decision will adversely impact many patients' quality of life. When not contraindicated, alternative strategies include co-prescription with other DMARDs, although there is evidence that once patients have responded to biologic therapy methotrexate may be withdrawn without loss of efficacy. There are broadly two groups of patients that cannot receive methotrexate: i) those in whom methotrexate is contra-indicated (including concurrent lung or liver disease, those with previous methotrexate-pneumonitis, and men/women planning a pregnancy); ii) those in whom methotrexate causes unacceptable side-effects. Both groups of patients would suffer unnecessarily if access to bDMARDs as monotherapy was withdrawn. Clinicians and patients would potentially find themselves in the unenviable position of not accessing bDMARDS, thereby suffering with progressive, disabling disease, or living with significant side-effects to therapy. Patients planning a family will be particularly affected, as current guidance suggests withdrawal of methotrexate at least 6 months before conception, for men and women. Removal of access to licensed bDMARDs as monotherapy will therefore mean patients living with active, disabling RA at a time when stable disease control is most desired. These are entirely avoidable scenarios and would represent a significant regressive step in the management of patients with rheumatoid arthritis. The ICER for bDMARDs in combination with methotrexate in patients at higher-risk of progressive disease is considerably lower than the base case ICER (£25,300 vs £41,600; Table 1 of Assessment Group Report, May 2015). We note however that the Assessment Group has not provided an equivalent ICER for those patients receiving bDMARD monotherapy at highest risk of progressive disease (Table 2 of Assessment Group Report, May 2015). We invite the committee to accept that monotherapy will be similarly more cost effective for those at highest risk of progression, and to recommend that bDMARDs should normally be prescribed in combination with methotrexate and should only be prescribed as monotherapy in those who are either intolerant or have a significant contraindication to methotrexate. *References were provided but not reproduced here.*	other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD. As a result of consultation the Assessment Group has calculated the ICER for the subgroup of patients with severe active rheumatoid arthritis, who cannot take methotrexate and who has the fastest HAQ progression. This scenario resulted in an ICER of £29,000 per QALY gained. For further discussions, please see section 4.84 of the FAD.

British Society for Rheumatology	**Lack of access to bDMARDs in patients with moderate disease** We consider it is an appropriate use of NHS resources to prescribe biologic drugs only for those who are most likely to have significant benefit. As discussed above we agree with the revised stricter eligibility criteria of active synovitis despite combination cDMARD therapy in those with a DAS>5.1. However, we also consider that failure of tight control in patients with moderate disease is a poor prognostic indicator. We are therefore concerned that: *'The Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group.'* We consider this conclusion to be unreasonable. The ICER from the exploratory analysis for the moderate group was only slightly higher than for the severe active group (£28,500 vs £25,300). For patients in the moderate group who have the 'fastest HAQ progression', the ICER of £28,500 falls within the cost effective range set by NICE. In order to understand the magnitude of the problem in those with moderate DAS scores, we commissioned a further independent analysis of the ERAS database. In the whole ERAS database (1465 patients) there were 602 patients with a high HAQ progression defined as ≥0.06 p.a. This may be an overestimate because of a number of patients with low data points who had HAQ progression rates as high as 1.5 or 2 that may have biased the analysis. Nevertheless we analysed the data to determine the number of moderate patients who had rapid HAQ progression. There were 120 patients treated with methotrexate who *always* had a DAS score between 3.2 and 5.1; there was only a modest rise in the average HAQ of 0.017 p.a. in this group. However, even in this cohort 39 patients (32.8%) had an average HAQ progression of ≥0.06 p.a. We also evaluated the cohort of patients with a *mean* DAS score between 3.2 and 5.1 - a total of 868 patients. There were 319 patients in this group who had rapid HAQ progression of ≥0.06 p.a. (36.8% of those with a mean DAS of 3.2 to 5.1 and 53% of all patients in the whole ERAS database with rapid HAQ progression). This data is in keeping with published evidence that the majority of damage occurs in patients with moderate disease. These data explain the reason for many European countries allowing patients with a DAS >3.2 to be eligible for bDMARDs and emphasise the fact that many patients defined as 'moderate' have a rapidly progressive course. They	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee discussed the criteria proposed by the BSR to identify people with rapid disease progression. The Committee was not persuaded that these alternative criteria to identify patients with the fastest HAQ progression could currently be used for decision making. The Committee concluded that further research is needed on the use of these criteria in combination with each other to identify patients with rapid disease progression, and the clinical effectiveness of treatment in the presence of these criteria. For further details please see section 4.94 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case estimate of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that alternative criteria to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.

	constitute a major clinical problem and should be considered for bDMARDs if they fail combination therapy. Rheumatologists in England and Wales would want to have the same clinical freedom as many European countries and prescribe bDMARDs to any patient with a DAS score of >3.2 who has failed combination cDMARDs. We would welcome the committee recommending this clinical freedom. However, we recognise that the committee wish to identify those who will have the fastest HAQ progression. Some risk factors for progression were identified in the ERAS study. However, more recent studies have found that one of the most useful predictors of progression is the anti-cyclic citrullinated peptide antibody (CCP or ACPA) that was unavailable during the data collection for ERAS. Several studies have now evaluated ACPA in predicting outcome in patients with rheumatoid arthritis. It is now clear that in addition to persistent active synovitis despite combination therapy, i) persistent elevation of inflammatory markers, ii) erosions on x-ray and iii) a positive ACPA are strong predictors of progressive disease. In clinical practice, rheumatologists target those who have all three factors for more aggressive therapy. The patients with a DAS 3.2 to 5.1 with these criteria who have failed combination therapy and steroids will have the fastest HAQ progression with an ICER calculated by the assessment group of £28,500. Although it is unlikely that these criteria will include all those with a moderate DAS who have progressive disease, it would identify the cohort of patients described by the Assessment Group with an ICER in the cost effective range. *References were provided but not reproduced here.*	
British Society for Rheumatology	There are additional data to indicate that long term costs will be reduced. In addition to the introduction of biosimilar drugs, there is increasing data to indicate that once patients are in remission, the dose of the bDMARD may be reduced in the majority of patients without loss of efficacy and many rheumatologists in the UK now follow EULAR guidelines and consider dose reduction in their treatment protocols. This practice has not been included in the Assessment Group analysis. We therefore invite the committee to reconsider their decision regarding patients with moderate disease, and recommend biologic treatment for those with a DAS score of 3.2 to 5.1 who have failed combination therapy and who have radiographic erosions, raised inflammatory markers and a positive ACPA (CCP). These are very strict criteria, and more demanding than those with a DAS>5.1, but we believe this to	Comment noted. The reduction in disease related costs have been considered in the Assessment Group's economic model. For further details please see section 4.68 of the FAD. The NHS costs of the biosimilar products currently available have been included in the analyses and did not change the Committee decision. For further details please see section 4.88 of the FAD. NICE can only consider treatments within their marketing authorisations which currently does not include dose reduction.

	be a reasoned and measured response in this group of patients and is fully supported by published evidence. *References were provided but not reproduced here.*	
Royal College of Pathologists	**Has all of the relevant evidence been taken into account?** The patients' and clinical experts' perspective that biological therapies have dramatically altered the course of rheumatoid arthritis, RA, contrasts with the analysis presented here that biologics are significantly better than intensive use of conventional agents only in severe disease after failure of conventional DMARDs. We too are convinced the Assessment Group's model has significant advantages over the modelling presented hitherto. However, the sensitivity analyses address technical issues rather than modelling whether plausible clinical effects of biologics are sufficient to reduce ICERs to acceptable levels, which may explain the difference in perspective. An established body of opinion advocates a paradigm shift in RA towards early intervention with biological therapies when high rates of remission are achievable. The early benefit of clinical remission would be further enhanced by the emerging option of dose reduction or cessation of the biological agent with a significant reduction in drug costs and infection risk. The potential impact of early, durable remission might be further magnified by a delayed effect on reducing the cardiovascular complications of RA which correlate with flares of active disease and the cumulative burden of disease severity. Thus early differences in treatment efficacy might assume increasing importance with time, which is particularly important given the model's lifetime scale. These data inform the likely ranges for key parameters to be tested for their potential impact on the base case assessment that biologics are not cost-effective as initial treatment for severe RA. Arguably, the potential impact of biologics on cardiovascular disease should also be subject to sensitivity analyses for moderate and severe RA after initial failure of DMARDs (see ID537 Committee papers #1060, #2167).	Thank you for your comment. No action required. NICE can only consider treatments within their marketing authorisations which currently does not include dose reduction or cessation. Clinical experts at the meeting indicated that the main interest in using the biological DMARDs is after the failure of methotrexate. For further details please see section 4.90 of the FAD The impact of biologics on cardiovascular disease was discussed at the meeting, but no evidence was provided that would allow this to be included in the economic modelling. The Committee recognised that the biologic DMARDs may have benefits on cardiovascular health. For further details please see section 4.109 of the FAD.
Royal College of Pathologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, for the evidence considered but please see above.	Comment noted, no actions required.

Royal College of Pathologists	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The recommendations are vulnerable to the argument that the model does not adequately address: i. The potential to reduce or withdraw biologics after inducing remission ii. The plausible impact on cardiovascular disease from either a. Early intervention with biologics in severe RA, OR b. Following failure of conventional DMARDs in moderate or severe RA It would be reasonable to ask the Assessment Group to carry out clinically relevant sensitivity analyses with the model to examine the validity of these concerns.	Comment noted. See responses above.
Merck Sharp & Dohme	We note that the Appraisal Committee has determined that the median cost-effectiveness estimate for biologic DMARDs likely falls between the Assessment Group base-case ICER for patients with severe disease (£41,600) and the Assessment Group ICER for patients with severe disease and the fastest HAQ progression (£25,300). A similar range of values was presented for moderate RA (base-case: £51,100 and fastest HAQ progression: £28,500) which suggested that biologic DMARDs could also be a cost-effectiveness intervention for moderate disease; however, the Appraisal Committee has concluded that the fastest HAQ progression analysis is not applicable to these patients. This appears to contradict the statements made by clinical experts who explained that "the initial DAS score does not define patients who progress fastest" or impact the likelihood of patients failing to respond to intensive conventional DMARD treatment who then require additional treatment options. Considering this, it is not clear why DAS score is still used to define eligibility for treatment. Access to these effective medicines was originally restricted to patients with severe RA due to cost implications, and it was acknowledged that those decisions would be reviewed at a later date with a view to widening access to a population with moderate RA. It is disappointing that this opportunity to widen access has been lost, especially when the cost of these drugs has reduced in real terms due to inflation since the original recommendations were made. The implication of losing this opportunity is that patients in the UK still have reduced access compared to their counterparts in other parts of Europe, with less stringent eligibility requirements. Given the considerations outlined in this	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case ICER of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly. For further details please see section 4.111 of the FAD.

	response, MSD urges the Appraisal Committee to revisit the issue of access to patients with moderate RA.	The Committee noted the limitation of the DAS response measures, however it concluded that that these are the most commonly used measures of disease response in the NHS in England. It was not persuaded that alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.94 of the FAD.
Merck Sharp & Dohme	Finally, Section 3.11 of the ACD states that for infliximab biosimilars "the contraindications, adverse reactions and administration schedule are the same as for infliximab". MSD would like to note that both infliximab biosimilars have black triangles, indicating the need for increased safety monitoring, whereas Remicade does not. The safety profile of both infliximab biosimilars is being continually assessed through the use of registries and post-marketing assessment, and very limited data exist on the safety of biosimilar infliximab when switching from Remicade.	Thank you for your comment, the relevant section of the FAD has been amended to reflect this.
Napp Pharmaceuticals	**Comments on changes to the draft scope** NICE has asked stakeholders if they would like to comment on the inclusion of the biosimilar infliximab (Remsima and Inflectra,) as an additional intervention in the scope and matrix of this multiple technology appraisal. Napp Pharmaceuticals Limited are naturally delighted that NICE has included Remsima®, into the draft scope. We were also pleased to be able to attend the last committee meeting on May 21st. NICE has recognised that the inclusion of Remsima represents an opportunity for the NHS to acquire infliximab at a much lower price. The lower price not only improves, obviously, the cost-effectiveness of this intervention but also allows the NHS to make savings which can be used to improve patient care. This could allow more patients to be treated with anti-TNF alpha inhibitors or to allow funding of alternative treatments either existing or innovative new medicines. We believe that NICE has a role to play in providing clarity with respect to the value of biosimilars, which we believe is something that local commissioners and clinicians are looking for to help local decision making. This may improve uptake and therefore help realise the opportunities highlighted above.	Comment noted, no actions required.
Napp	**The Appraisal Committee request for comments**	Comment noted. The Committee did not consider

Pharmaceuticals	We note from the consultation document that The Appraisal Committee is interested in receiving comments on the following: • **Has all of the relevant evidence been taken into account?** • **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We believe that there has been every attempt to take the evidence into account. However we note that there have been concerns raised about the use of a cut-off point for the disease activity score (DAS28) score of 5.1 Clinicians and patient groups have suggested that some patients may have a lower DAS score yet have persistent synovitis, and may do badly if not treated early enough with TNF-alpha inhibitors. Patients may experience pain, disability and loss of function that may not have been picked up in scoring systems yet contribute to a substantial loss of quality of life and potential societal costs. These patients may benefit from the use of TNF-alpha inhibitors before a DAS score of 5.1 is reached. Indeed we believe from reading the ACD that The Committee not only understands this but is empathetic to this situation. We would hope that it will be able to find a pragmatic approach to dealing with the somewhat arbitrary cut-off point of 5.1. We would support a more flexible approach to patient selection that would allow those patients classified as having moderate to severely active disease access to these medicines provided they have had prior treatment with conventional DMARD therapy. This would allow the clinicians the opportunity to apply their judgement and use a trial of TNF-alpha inhibitor treatment with close monitoring and within the confines of a "stopping-rule."	that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case ICER of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly. For further details please see section 4.111 of the FAD. The Committee noted the limitation of the DAS response measures, however it concluded that that these are the most commonly used measures of disease response in the NHS in England. It was not persuaded that alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.94 of the FAD.
Napp Pharmaceuticals	**Comments on the preliminary recommendations**. **1.1** and **1.4** We note with interest that The Committee has recommended (1.4) that the lowest price medicine should be used where appropriate and with the provisos as stated. We support this view however, we would like to suggest that NICE finds a way	Comment noted. Section 1.5 of the FAD indicates that the least costly product should be used. Because the prices for infliximab biosimilars are negotiated through the NHS commercial medicines unit an additional bullet point in section 1.1 was not needed. No changes to the FAD.

	to sign post stakeholders, particularly payers and prescribers, to the lower acquisition prices possible through the procurement tender process. This could be done as a footnote to recommendation 1.4 or as an extra bullet point in 1.1. For the latter we would suggest: • and that the companies supplying biosimilar infliximab (Remsima and Inflectra) should at least maintain the agreed discounted procurement prices.	
Napp Pharmaceuticals	**2.4** We suggest that the phrase “more recently,” is slightly an inaccurate statement as these biological medicines were introduced more than 10 years ago,	Thank you for your comment the wording of the FAD has been amended.
Napp Pharmaceuticals	**3.1** After the sentence “A biosimilar medicine is a medicine that is developed to be similar to an existing biological medicine”. Please consider inserting: In line with European Medicines Agency (EMA) requirements, biosimilars undergo an extensive comparability exercise to demonstrate that they have comparable physicochemical properties and biological activity as the originator product.	Thank you for your comment. This level of detail was not necessary for the background section of the FAD.
Napp Pharmaceuticals	**3.11** We suggest that it would be useful to clarify that the indication for infliximab (both Remicade and the biosimilars Remsima and Inflectra) is identical. For example: Infliximab biosimilars (Remsima, Napp Pharmaceuticals and Inflectra, Hospira UK), in combination with methotrexate, have precisely the same UK marketing authorisations as Remicade, namely for the reduction of signs and symptoms as well as the improvement in physical function in adults with active disease when the response to DMARDs, including methotrexate, has been inadequate……..	Thank you for your comment the wording of the FAD has been amended.

Napp Pharmaceuticals	**3.12** We note that NICE refers to net price when referring to the cost of medicines. This is factually incorrect as it is the NHS list price. In the case of the Remsima this would be the gross price and the net price would be the true acquisition price through the negotiated tender prices which will be at least [redacted] and up to [redacted] lower than the NHS list price for Remicade. We suggest revising the text to read The NHS list price of infliximab biosimilars is £377.66 per 100-mg vial (information provided by the companies). Assuming a weight per person of 70 kg, no vial wastage, and 3 initial doses in the first year followed by treatment every 8 weeks, the cost in the first year is £6344.69, and then £5155.06 per year. Actual acquisition costs may vary significantly in different settings because of negotiated procurement discount. We would also like to point out that infusion costs vary by hospital and if given as home infusions the treatment is VAT exempt.	Comment noted. The FAD has been amended to reflect this and the contract prices of the infliximab biosimilars have been considered in the analyses. For further discussion please see section 4.88 of the FAD.
Napp Pharmaceuticals	**4.2.43** We note that the Assessment Group (AG) has taken into account all patient access schemes. The AG may not have considered the lower acquisition costs associated with Remsima through the tender process. We are however conscious that this would not have changed the preliminary recommendation of The Committee which includes infliximab as a treatment option. Including the tender price would only serve to reinforce the value of infliximab biosimilars to the NHS.	Comment noted. As a result of the consultation on the ACD, the Assessment Group did further exploratory analyses and investigated the impact of using the contract prices for the infliximab biosimilars on the ICER for infliximab in the methotrexate-experienced subgroups who also can have methotrexate. For further discussion please see section 4.88 of the FAD.
Napp Pharmaceuticals	The average administration cost per subcutaneous injection of £3.05 seems very low. Did the AG take into account the costs of patient education, nurse support and clinic visits for those biologics administered subcutaneously rather than simply consider that such patients were not carefully monitored (which comes at a cost)?	Thank you for your comment the cost calculations in the model were discussed at the Committee meeting. The Committee heard from the Assessment Group that different administration costs were not modelled. However, the model is not sensitive to small changes in drug or administration costs. This is shown in the sensitivity analyses using alternative drug acquisition costs. The main drivers of the cost effectiveness

		were the HAQ progression rates, HAQ utility mapping function and discounting rates.
Napp Pharmaceuticals	**4.2.75** The AG has carried out an analysis using the NHS list price for Remsima and Inflectra, infliximab biosimilars, which has had the effect of reducing the ICER by approximately 7%. We would suggest that in future appraisals that tender prices could be used in a sensitivity analysis as this would have a greater effect on the ICER. The Committee mentioned that the NHS list price was only 10% lower than the originator infliximab whereas the negotiated tender prices will be at least [redacted] and up to [redacted] lower than the originator (Remicade) NHS list price. This would have a considerable effect on the ICER.	Comment noted. As a result of the consultation on the ACD, the Assessment Group did further exploratory analyses and investigated the impact of using the contract prices for the infliximab biosimilars on the ICER for infliximab in the methotrexate-experienced subgroups who also can have methotrexate. For further discussion please see section 4.88 of the FAD.

Napp Pharmaceuticals	**4.3.5** We note that The Committee has recognised the issues for people with a DAS score of below 5.1 or those who have contra-indications to conventional DMARDS. The Committee also recognised the clinical interest in the use of biological DMARDS for people with moderate disease. It is disappointing that The Committee was unable to make a recommendation for this group of people that would allow them access to the use of biological DMARDS, we would like to suggest that further consideration should be given to the criteria that would allow access to these life changing treatments.	Comment noted. The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD. For the population with moderate active disease the Committee was not persuaded that the analysis of fastest HAQ progression was as applicable as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case ICER of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly. For further details please see section 4.111 of the FAD.
Napp Pharmaceuticals	**4.3.10** The Committee may not be aware of the potential NHS savings that could be made by switching from originator infliximab to biosimilar infliximab. Furthermore The Committee should be made aware of the active switch programmes and recent policy changes relating to the use of biosimilars in other countries such as Australia1, Finland2 and The Netherlands3. We would suggest that statements such as: "However, if a person is already on a treatment and their disease is responding, they would not be switched to a	Comment noted. This sentence reflects clinical expert opinion and has not affected the appraisal recommendations which do not include switching treatments.

	biosimilar" could hinder uptake of biosimilars in the UK. This opinion is not universally held within the UK clinical community, and a number of centres are already actively switching RA patients from originator to biosimilar infliximab4. Furthermore this opinion is not based on robust scientific evidence, as the EMA has authorised biosimilar infliximab as having no clinically relevant difference to originator infliximab5. In Norway 62% of patients are now being treated with Remsima, which includes a significant number of switch patients from originator to the significantly less expensive biosimilar6. In the extension phase of the PLANETRA rheumatoid arthritis study patients treated with Remicade up to week 54 were allowed to switch to Remsima and were followed for up to 102 weeks. There were no reported significant differences in response or side-effects. We wish to point out that the use of subcutaneous injections of do not obviate the need for other costs. There are costs associated with education, support and clinical reviews of these patients on subcutaneous doses rather than intravenous infusions where problems are picked up sooner avoiding extra hospital clinic visits. We wish to reiterate that the NHS list price is not indicative of the true acquisition price of Remsima in the UK. We are therefore disappointed to see comments such as "…was only 10% less…"and "….only a small reduction in in the ICER…." We would reiterate our point made earlier that commissioners and clinicians are looking to bodies such as NICE and MHRA to provide clarity on this topic at this time. In reality the true acquisition price for biosimilars through the procurement tender process is substantially lower at [redacted] below the originator list price of £419.62; which would in turn lead to a much lower ICER than that quoted.	The cost calculations in the model were discussed at the Committee meeting. The Committee heard from the Assessment Group that different administration costs were not modelled. However, the model isn't sensitive to small changes in drug or administration costs. This was shown in the sensitivity analyses using alternative drug acquisition costs. The main drivers of the cost effectiveness were the HAQ progression rates, HAQ utility mapping function and discount rates. As a result of the consultation on the ACD, the Assessment Group did further exploratory analyses and investigated the impact of using the contract prices for the infliximab biosimilars on the ICER for infliximab in the methotrexate-experienced subgroups who also can have methotrexate. For further discussion please see section 4.88 of the FAD.
Napp Pharmaceuticals	**4.3.18** The AG's exploratory analysis in sections 4.2.74 - 4.2.75 incorporated the price of the biosimilars and The Committee noted that this did not alter the base case ICERs substantially. We contend that the AG should have used the negotiated tender prices which will be at least	Comment noted. As a result of the consultation on the ACD, the Assessment Group did further exploratory analyses and investigated the impact of using the contract prices for the infliximab biosimilars on the ICER for infliximab in the methotrexate-experienced subgroups who also can have

	[redacted] lower than the list price for Remicade £419.62 which we suggest would have altered the ICER more significantly.	methotrexate. For further discussion please see section 4.88 of the FAD.
Napp Pharmaceuticals	**4.3.22** We would like to understand whether the ICERs quoted in this section were calculated using only list prices or whether PAS where appropriate for some products and tender prices for the biosimilars were included. Home therapy infusions could also have a saving of 20% by being VAT exempt. We are disappointed that those patients with moderate disease but with fast HAQ progression are still being denied access to biological DMARDS on the basis of a QALY of £28,500. We would suggest this is likely to be lower if the true price for the biosimilars had been included.	The ICERs quoted in the FAD are the median ICERs for the products as a group. The Assessment Group indicated that the inclusion of the infliximab contract price wouldn't affect the median ICER because the ICER for infliximab using the list price is lower than the median ICER for the products as a group. The Assessment Group completed separate analyses and presented an ICER for infliximab biosimilars compared to methotrexate that was discussed by the Committee. This ICER did not alter the Committees decision. For further discussion please see section 4.111 of the FAD.
Napp Pharmaceuticals	**Summary of Conclusions Table** <u>The Committee's recommendations:</u> We suggest a minor amendment to this sentence beginning: "Start treatment with……." so that it reads: Start treatment with the least expensive drug (taking into account: local acquisition discounts, administration costs, dose needed and product price per dose).	Comment noted the wording of the FAD has been amended.
Napp Pharmaceuticals	<u>Evidence for cost-effectiveness.</u> Most likely cost-effectiveness estimate (given as an ICER) The Committee concluded that biological DMARDs were a cost-effective use of NHS resources only for people with severe active rheumatoid arthritis previously treated with methotrexate. For people with moderate active disease previously treated with methotrexate and with severe active disease not previously treated with methotrexate It concluded that biological DMARDs were not cost effective.	For the population with moderate active disease the Committee was not persuaded that the analysis of fastest HAQ progression was as applicable as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case ICER of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee

<table>
<tr>
<td></td>
<td>They also could not be considered as a cost-effective use of NHS resources when used as monotherapy.

Whilst we agree with the first point above, we do not agree that the current suggestion of a cut-off point for the DAS score of 5.1 is fair to all patients with moderate disease. We also feel that recognising the lower tender prices as the true acquisition costs of biosimilar infliximab projects more realistic conclusions about which medicine option should be taken for NHS patients.</td>
<td>was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly. The Committee noted the reduction in the ICER to £37,600 per QALY gained for biosimilar infliximab, and the availability of infliximab biosimilar but this did not change its decision. For further discussion please see section 4.111 of the FAD.</td>
</tr>
<tr>
<td>Napp Pharmaceuticals</td>
<td>Table Section 4 page 72
<table>
<tr><th colspan="3">Additional factors taken into account</th></tr>
<tr><td>Patient access schemes (PPRS)</td><td>Four patient access schemes were taken into account, for tocilizumab, abatacept, golimumab and certolizumab pegol.</td><td>4.2.43</td></tr>
<tr><td>End-of-life considerations</td><td>None</td><td>–</td></tr>
<tr><td>Equalities considerations and social value judgements</td><td>There were no equality issues raised during the Committee discussion.</td><td>4.3.25</td></tr>
</table>
We believe that the use of PPRS is inappropriate here and may have the potential to mislead the reader that the rebates being paid by the Pharmaceutical Industry are being taken into account in health economic evaluations.

We suggest the following amended table should be used:
<table>
<tr><th colspan="3">Additional factors taken into account</th></tr>
<tr><td>Patient access schemes (PAS)</td><td>Four patient access schemes were taken into account, for tocilizumab, abatacept, golimumab and certolizumab pegol.</td><td>4.2.43</td></tr>
<tr><td>Biosimilar acquisition prices</td><td>Only the NHS list price was used not the NHS tender acquisition price</td><td>4.3.10</td></tr>
</table>
</td>
<td>Comment noted. This is a standard template. No changes to the FAD made.</td>
</tr>
</table>

	End-of-life considerations	None	–		
	Equalities considerations and social value judgements	There were no equality issues raised during the Committee discussion.	4.3.25		
Napp Pharmaceuticals	**5.4** We note with interest that the agreement between the DH and companies offering patient access schemes has been mentioned. We suggest that NICE considers adding a comment here to reflect that the biosimilars are also available to the NHS at substantial discounts below the NHS list price.				Comment noted. Because the prices for infliximab biosimilars are negotiated through the NHS commercial medicines unit, the contract prices for infliximab biosimilars do not need to be added to this section. No changes to the FAD.
Napp Pharmaceuticals	**5.5** Implementation support tools are a recognised part of NICE guidance. It would be useful if examples in the costing template could reflect a range of prices for biosimilars rather than only include calculations based purely on NHS list price.				Comment noted. Any costings and implementation tools would include a publically available price and provide flexibility for trusts to amend.
Hospira	The biological disease-modifying anti-rheumatic drugs (DMARDs) adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, each in combination with methotrexate, are recommended as options for treating rheumatoid arthritis for severe disease that has not responded to intensive therapy with a combination of conventional DMARDs (NICE draft guidance [ID537], 2015). Conventional DMARDs include methotrexate, leflunomide and sulfasalazine. NICE technology appraisal draft guidance (NICE draft guidance [ID537], 2015) recommends the use of the above biological DMARDs in patients with rheumatoid arthritis who have a disease activity severity (DAS28) score greater than 5.1. The draft guidance does not recommend the use of biological DMARDs in previously untreated disease. It further states that the cheapest option should be used, taking into account administration costs, required dose, and product price per dose.				Comment noted, no actions required.
Hospira	The annual costs of treatment with each of the biological DMARDs under consideration are summarised in Table 1. *Table 1 has been received but not reproduced in the table*				Comment noted, no actions required.
Hospira	Inflectra (biosimilar infliximab) has demonstrated comparable clinical efficacy to				Comment noted. As a result of the consultation on

	Remicade (originator infliximab) (EMA [Inflectra], 2015). The contraindications, adverse reactions and administration schedule for Inflectra are the same as for Remicade (NICE draft guidance [ID537], 2015). The Appraisal Committee's preliminary recommendations acknowledge that the costs of Inflectra may vary in different settings because of negotiated procurement discounts. However, the Appraisal Committee considered the list price of Inflectra, which is 10% less than that of the originator product. The resulting small reduction in the incremental cost-effectiveness ratio (ICER) led to the conclusion that the availability of biosimilar treatments is not a key driver of cost effectiveness (NICE draft guidance [ID537], 2015). It is understood that this appraisal will make a recommendation for the use of Inflectra in the indication of rheumatoid arthritis for severe disease that has not responded to intensive therapy with a combination of conventional DMARDs, as it has been included in the scope of this appraisal (NICE draft guidance [ID537], 2015). However, from recent correspondence with NICE, Hospira understands that Inflectra has not been included in the Assessment Group's economic model. Due to the late inclusion of Inflectra in the scope of this appraisal, the timelines have not allowed for Hospira to develop an economic model. Hospira is concerned that the assertion that Inflectra is not a more cost effective treatment option compared with Remicade (NICE draft guidance [ID537], 2015; section 4.3.10), is not justified, based on its exclusion from the Assessment Group's model. Furthermore, using the tender prices would lead to an even lower ICER compared with Remicade than when the Inflectra list price is used, rendering the treatment even more cost effective. This could have a considerable effect on treatment costs over the lifetime treatment of patients. Thus using Inflectra in preference to Remicade could provide cost savings to the National Health Service (NHS). Hospira requests that the Appraisal Committee take into consideration that Inflectra is offered across a range of in-market tender (contract) prices based on the size of the regional market. The tendering process for Inflectra is complete and the tender prices are now available. The lowest Inflectra in-market tender price of [redacted] is at [redacted] discount of the Remicade list price; the highest Inflectra in-market price [redacted] is at [redacted] discount of the Remicade list price. Hospira suggests that the Assessment Group consider in-market tender prices for Inflectra in the appraisal as they represent the actual cost to the NHS in clinical practice.	the ACD, the Assessment Group did further exploratory analyses and investigated the impact of using the contract prices for the infliximab biosimilars on the ICER for infliximab in the methotrexate-experienced subgroups who also can have methotrexate. For further discussion please see section 4.88 of the FAD.

	Although Remicade is offered at around a 15% discount to the list price through the tender frameworks, there is the stipulation that at lower volumes (agreed individually with each trust or clinical commissioning group), the price of Remicade would increase. Therefore it would be appropriate to model the cost-effectiveness based on the list price of Remicade. Finally, Hospira would like the Committee to consider that precedent was set in the approach of using in-market tender prices with the NICE technology appraisal of erythropoiesis‑stimulating agents (ESAs) [TA323]; (NICE final guidance [TA323], 2014). In a scenario analysis, the Assessment Group applied the best contract prices (those reflecting the highest discounts from list price) available for the ESAs to its base-case analysis, rather than the prices listed on the British National Formulary. The Committee concluded that the contract prices of the ESAs were the most relevant prices as they reflected the actual prices paid by the NHS for ESAs based on a 'price‑volume' agreement with the companies (NICE final guidance [TA323], 2014).	
Pfizer	Pfizer would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We welcome the interim recommendation that etanercept in combination with methotrexate continues to be considered a cost effective use of NHS resources for severe rheumatoid arthritis (RA) patients previously treated with methotrexate. Despite the positive recommendation for combination therapy in severe RA patients previously treated with methotrexate, we are concerned that errors continue to be identified in the Assessment Group (AG) economic model, the most recent of which resulted in a change in cost per quality-adjusted life-years (QALYs) of approximately £20,000. In addition, Pfizer believes that limitations with the AG analyses have led to an underestimation of the cost-effectiveness of biologic disease modifying anti-rheumatic drugs (DMARDs) as outlined in Pfizer's previous consultation responses.	Comment noted. The Committee accepted that the Assessment Group model was appropriate to use for decision-making purposes. For further discussion please see section 4.98 of the FAD.
Pfizer	Pfizer continues to be confident that etanercept is a cost-effective treatment for all patients included in the scope of this appraisal. Therefore, we are disappointed that the Committee have issued preliminary recommendations that the use of etanercept for patients with moderate-to-severe RA previously treated with methotrexate and as monotherapy are not considered a cost-effective use of NHS resources. The preliminary monotherapy recommendation differs from the current published guidance issued by NICE in	Comment noted. The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active

	the Multiple Technology Appraisal (MTA) of adalimumab, etanercept and infliximab for the treatment of RA (TA130) in 2007, which states: "TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy." This change will lead to inequitable access to biologics for patients with severe RA who are intolerant of methotrexate or for whom methotrexate is considered to be inappropriate. Consequently, surgery will become the only treatment option following failure of conventional DMARDs for these patients. More importantly, Pfizer believes that the preliminary recommendation to be unreasonable as important evidence has not been fully considered by the Committee, which has led to an over-estimation of the plausible incremental cost effectiveness ratio (ICER) for biologic DMARD monotherapy in severe RA patients. The main reasons for this over-estimation of the plausible ICER are based on the following three important factors: i. The efficacy data used by the AG to inform the comparator sequence in the assessment of biologic DMARD monotherapy in severe RA patients previously treated with methotrexate may over-estimate the treatment effect of sulfasalazine. The sequences presented in Table 159 in the Updated Technical Assessment Report (TAR) suggest that the AG compared monotherapy biologic DMARDs to a sulfasalazine and non-biological therapy strategy. However, after review of the AG base case European League Against Rheumatism (EULAR) network (Updated TAR Table 19), it is clear that methotrexate is used in the control arm for each trial (n=8) that informed the efficacy estimates for conventional DMARDs in the economic model. Given that methotrexate has been recognised as potentially the most effective conventional DMARD (Emery 2000, NICE CG79, Pincus 2003, Smolen 2013), it is likely that the effectiveness of sulfasalazine has been overestimated. Consequently, Pfizer believe that the cost-effectiveness of biologic DMARD monotherapy for patients with severe RA previously treated with methotrexate has been underestimated, and will be lower than the current AG base case ICER of £48,300 (Pfizer cannot quantify the impact of this error on ICERs without an updated AG network meta-analysis).	rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.
Pfizer	ii. In Section 4.3.20 of the ACD report the Committee states that the most plausible ICER for combination therapy in severe RA patients previously	As a result of consultation the Assessment Group has calculated the ICER for the subgroup of patients

	treated with methotrexate was likely to lie between the AGs base case ICER (£41,600) and the ICER for the fastest Stanford Health Assessment Questionnaire (HAQ) progression (£25,300). However, a comparable analysis was not provided for severe RA patients who require monotherapy biologic DMARDs. Pfizer believe that this subset may also experience rapid disease progression. We would suggest that the resulting ICER would lie between those from comparable analyses for severe and moderate RA treated with combination therapy (£25,300 and £28,500 respectively). If calculated this estimate would provide the Committee with an ICER range and more accurate information upon which to consider the most plausible ICER for monotherapy. iii. Finally, the Committee explain in Section 4.3.23 of the ACD report that ICERs for monotherapy biologic DMARDs were higher than combination biologic DMARD therapy. The Committee clarify that differences in ICERs were primarily driven by the increased cost of replacing rituximab in combination with methotrexate with a subsequent line of monotherapy biologic. Pfizer is concerned that the decision not to recommend monotherapy biologic DMARDs as a cost-effective use of NHS resources is driven by the inclusion of specific treatments further down the treatment care pathway. This suggests that sensitivity analyses undertaken by the AG (presented in the company papers prepared ahead of the 2nd Committee meeting – dated 21/05/2015) may not have fully addressed this issue. Furthermore, the implausibility of the ICERs is emphasised by the similarity of efficacy estimates presented by the AG for monotherapy and combination therapy in both the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) evidence networks. As a result, Pfizer believes that the ICER considered most plausible by the Committee for etanercept monotherapy in severe RA patients has been over-estimated. Pfizer therefore considers the preliminary recommendation to be unreasonable. The economic estimates provided in our original submission remain the most plausible and demonstrate that etanercept monotherapy continues to be a cost-effective treatment option. Therefore, the Committee should reinstate etanercept monotherapy for this subset of the severe RA patient population to ensure equitable access to appropriate treatment.	with severe active rheumatoid arthritis, who cannot take methotrexate and has the greatest HAQ progression. This scenario resulted in an ICER of £29,000 per QALY gained. For further discussions, please see section 4.84 of the FAD. Comment noted. The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.
AbbVie	**Section 1. Has all of the relevant evidence been taken into account?** ***1.1*** *Change in the quality of life has been inadequately captured, underestimating the health gain with biologics.*	Comment noted.

	AbbVie considers that the changes in quality of life with biologic treatments were not adequately captured in this appraisal. We outline the reasons below.	
AbbVie	**1.1.1 Relationship between pain levels and HAQ scores** AbbVie welcomes the acknowledgement by the Assessment Group that they identified and corrected an error in their modelling following the feedback from AbbVie on the poor fit for the relationship between HAQ and pain. However, it does not appear that the remainder of AbbVie's comments on the relationship between pain levels and HAQ scores were considered. To reiterate: The data from the Research in Active Rheumatoid Arthritis (ReACT) study suggest that the impact of anti-TNF therapy on reducing pain may be underestimated in both the manufacturer and AG modelling, given that pain is not modelled independently from the modelling of HAQ improvement and is not considered to systematically differ between patients on different therapies. We illustrate this graphically below. *Figure1 has been received but not reproduced in the table.* These figures clearly show that the mean pain VAS is systematically higher at baseline compared to all levels of HAQ score when all observations are used (graph on the left vs. graph on the right). As the majority of patients at baseline (graph on the left) were on cDMARD therapy but had disease that was considered severe enough (DAS28>3.2) to require adalimumab therapy, they can be considered to be similar to patients in the appraisal who would continue on cDMARD, whereas patients on biologics are best represented by the graph on the right. It is hypothesised that the difference between the baseline and all observation data is attributable to the impact of adalimumab therapy on reducing the pain associated with RA. However, neither AbbVie nor the Assessment Group modelled different effects for the different treatment groups. As result of not differentiating between cDMARDs and biologics, the benefits of biologics have not been fully captured in the Assessment Group model and AbbVie requests that the Committee take this into consideration before making	During the meeting the Committee has discussed the methodology used by the Assessment group for obtaining EQ-5D from HAQ scores. It concluded that it was appropriate for decision-making. The Committee recognised that the biologic DMARDs can improve pain. For further discussion please see section 4.106 of the FAD.

	conclusions on the most appropriate the ICER for patients with moderate RA.	
AbbVie	**1.1.2 Psychological benefit of being in work** AbbVie notes comments sent to the Committee by the National Rheumatoid Arthritis Society (NRAS) highlight that patients consider it vital to stay in work not only for economic reasons, but also because of the psychological impact on patients: "*In a survey…. – 88 per cent of respondents said that having a job helped them cope with the disease with incidences of depression significantly higher among non-workers than workers".* AbbVie questions whether the emotional benefit of being able to return to work has been adequately captured in the methods used to calculate the QALYs and should the Committee consider this not to be the case, then the ICERs would be improved for the biologic treatments.	Thank you for your comment. In making their recommendations the Committee recognised the psychological benefits of biological DMARDs for patients and their families. For further discussion please see section 4.111 of the FAD.
AbbVie	**1.1.3 Risk of cardiovascular events among RA patients and benefits of biologic therapy** AbbVie would again like to highlight the cardiovascular (CV) benefit of biologic treatments in RA patients, a point also raised by the British Society of Rheumatology (BSR) during the appraisal, but which we do not think have been considered by the Committee. A systematic review of the evidence on CV risk and management thereof prompted the European League Against Rheumatism (EULAR) to issue evidence-based recommendations for the CV risk management in RA. Amongst their findings were that the standardised mortality ratios are increased in RA patients and range from 1.5 to 1.9, with the increased risk of mortality in these patients mostly attributed to CV disease. These recommendations further note the necessity of early and effective control of disease activity to lower the CV risk in RA patients. Several studies have demonstrated the value of using anti-tumour necrosis factors (anti-TNFs) in risk reduction for CV disease among RA patients. A meta-analysis of 1,411 patients from four Phase II/III clinical trials of adalimumab (i.e., ARMADA, DE019, PREMIER, and OPTIMA) reported a 66%	Thank you for your comment. The impact of biological DMARDs on cardiovascular disease was discussed at the meeting. The Committee recognised that the biological DMARDs may have benefits on cardiovascular health. For further details please see section 4.109 of the FAD.

	reduction in the hazard of major adverse CV events (MACEs) and 84% reduction in the hazard of nonfatal myocardial infarction among the adalimumab+MTX group compared to MTX monotherapy group. In another example, a study using a large real-world registry evaluated the association between using anti-TNF therapy and risk of CV events (composite outcome of myocardial infarction, transient ischaemic attack or stroke and CV-related death) in 10,156 RA patients. This study reported a 61% hazard reduction in CV events among RA patients who used anti-TNFs compared to patients treated with cDMARDs. Another study retrospectively examined 113,677 RA patients from the administrative claims database and reported use of anti-TNF therapy to significantly reduce the cumulative risk for any studied CV event (myocardial infarction, stroke, unstable angina, or congestive heart failure) by 21%, 38% and 51% over years 1, 2, and 3, respectively, compared to patients without anti-TNFs. These benefits have not been adequately captured within the methodology employed by either the manufacturers or Assessment Group and as results may have underestimated the QALY gains of anti-TNFs. AbbVie requests that the Committee bear this in mind during their deliberations.	
AbbVie	**1.1.4 Changes in HAQ score can influence mortality** AbbVie welcomes the acknowledgement by the Assessment Group that if it can be proven that changes in HAQ did influence mortality, this would improve the cost-effectiveness of biologics. To this effect, AbbVie would like to point out that in the publication used by the Assessment Group to determine relationship between HAQ and mortality; the authors reported that an improvement in HAQ of ≥0.5 units was associated with a significant reduction in mortality risk over all time-periods from six months through to three years. Similarly HAQ worsening was always associated with increased mortality risk. More recently Ajeganova et al. investigated the relationship between disease activity (which has elsewhere been shown to be significantly correlated to HAQ) over the first two and five years of RA and risk of mortality using the BARFOT cohort. They found that the hazard ratio for mortality for those with persistent disease activity was 1.7 times higher (1.1-2.4), and for those in intermittent remission 1.6 times higher (1.02-2.4) than for those in sustained remission. They concluded that persistent disease activity and intermittent	Comment noted, the relationship of HAQ score and mortality were discussed at the meeting, but the Committee thought they would not alter the decision.

	remission during the first years after diagnosis of RA increased the risk of mortality independently of factors such as age, gender, smoking and treatment regimen. Thus there is evidence to suggest that changes in HAQ and disease activity affect mortality risk. As previously pointed out by AbbVie, the assumption used in the Assessment Group model that only baseline HAQ predicts mortality, may be a source of bias in the results as it ignores the effect of a more favourable HAQ progression for patients on biologics. This result in underestimation of additional survival provided by biologics over cDMARDs and AbbVie trusts the Committee will consider this relevant to the cost-effectiveness evaluation.	
AbbVie	***1.2*** *Limited consideration of the interventions' value to society* AbbVie welcomes the acknowledgement within the ACD that RA is associated with not only substantial direct costs, but also indirect costs such as reduced productivity (Section 2.1) and can have a significant effect on the lives of patients and their family (Section 4.3.1). As the committee is aware, cost–utility analysis cannot be the sole basis for NICE's decisions and committees should use their judgement about the acceptability of an intervention as an effective use of NHS resources taking into account amongst others, the social value thereof. Whilst AbbVie understands that benefits to society are not incorporated through the Institutes' reference case, which only considers the direct cost incurred by the NHS and benefits to the patients, AbbVie would still like to point out that no consideration was given to capturing the benefits of biologics on wider societal benefit through a scenario analysis in the Assessment Group model. AbbVie therefore believes that the committee should give further consideration to the evidence regarding wider societal benefits which are presented below.	Thank you for your comment. The appraisal has been conducted in the context of the NICE reference case to include an NHS and PSS perspective. Scenarios capturing benefits to other government departments are considered only with agreement from the Department of Health, usually before referral of the topic. Productivity costs are not included.
AbbVie	**1.2.1 Indirect cost** The importance of work participation is also emphasised in the Treat-To-Target recommendations in RA, which suggest that participation in work is an integral	Thank you for your comment. The assessment has been conducted in the context of the NICE reference case to include an NHS and PSS perspective. Productivity costs are not included. Costs to

	part of the primary goal of treating RA patients. As also discussed in our submission and by the BSR and NRAS, there is an abundance of evidence of the effects of RA on the wider costs to society, and in particular, work participation. This evidence shows that the cost of sick leave due to work related disability is substantial and that many patients are forced to leave employment due to their disease. Loss of productivity and high absenteeism due to the debilitating effect of RA has indirect costs to society, as does other costs such as caring for a family member or friend with RA and costs incurred by patients purchasing aids and devices to assist with reduced mobility caused by RA. The relative importance of these costs with respect to direct medical costs cannot be understated, and a report where these are not mentioned gives only a partial view of the true cost-effectiveness estimates of treatments. For this reason AbbVie included in its submission sensitivity analyses which examined the effect of including costs due to the loss of work capacity. In these scenarios the ICER for moderate RA decrease by 36% (from £18,792/QALY to £11,964/QALY) and the ICER in the severe RA group by 35% (from £16,650/QALY to £10,905/QALY). Of note is that these analyses do not represent the entire spectrum of indirect costs incurred by patients with RA or wider societal costs, and thus incorporating additional societal costs such as cost to carers, state funded disability benefits and home adaptations will decrease the ICER even further. Therefore, due to the importance of work participation and the considerable impact of indirect costs thereof, AbbVie requests that the Committee consider the value of biologics to society as part of their decision.	caregivers may be included where these might otherwise have been provided by the NHS, but no such evidence was provided that could be included in the economic model. The Committee recognised the effect of rheumatoid arthritis to patients and their families and took account of this in their decision making. See FAD sections 4.90 and 4.111.
AbbVie	**1.2.2. Non-clinical and non-cost benefits** It is unfortunate that the current NICE process cannot fully take into consideration some of the non-clinical and non-cost benefits associated with biologic treatments, but AbbVie would like to draw the Committee's attention to some of the benefits experienced by patients, as voiced through NRAS: *"Another aspect of the disease that is frequently overlooked is impact on the family. Our own research has found that when a person's partner has RA this is likely to have negative impacts for the person on: their domestic*	Thank you for your comment. The Committee recognised the effect of rheumatoid arthritis to patients and their families and took account of this in their decision making. See FAD sections 4.90 and 4.111.

	responsibilities; their employment choices and the family finances; their social life; their relationship with their partner including their sex life; and their own emotional wellbeing. Children with a parent who has RA are also likely to be affected by this into their adulthood." Whilst these benefits cannot be directly quantified to the NHS, AbbVie would nonetheless call on the Committee to use their judgement about the acceptability of biologics as an effective use of NHS resources taking into account the non-clinical and non-cost benefits.	
AbbVie	**1.3 Limited consideration of alternative discount rates allowed by the NICE Methods Guide** AbbVie notes that the Committee considered the 3.5% discount rate to be in line with the current NICE Methods Guide (Section 4.3.1). As the Committee would be aware, Section 6.2.19 of the NICE Methods Guide allows alternative discount rates to be considered *"in cases when treatments restore people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years."* and *"…if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved."*. The Methods Guide also goes on to state that *"…the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."* Whilst the ACD states the Committee discussed that the discount rates were inconsistent between the original guidance and that they were aware of the economic rationale for equal discount rates for costs and benefits, it does not appear that the Committee considered alternative ICERs based on discount rates of 1.5% for costs and benefits as permitted in the Methods Guide. AbbVie understands that this would not have been possible as the Assessment Group did not present a scenario using these discounts rates specifically. The BSR in this appraisal has stated that the *"management of RA has been revolutionised by the introduction of biologic treatments"* and that biologics are *"highly effective"*. Furthermore, they indicated that since the introduction of biologic therapies in 1999 there is *"…evidence of a reduction in inpatient*	Comment noted. The Committee discussed whether the alternative discount rates described in section 6.2.19 of NICE guide to the methods of technology appraisal would apply to rheumatoid arthritis. It understood that the criteria in the methods guide were for use when the costs of a treatment were accrued at the beginning of treatment, but the benefits only accrued in the long term. It concluded that the circumstances described in the methods guide were not applicable for situations of ongoing treatment. For further discussion please see section 4.106 of the FAD.

	treatment and orthopaedic surgery in patients with RA". NRAS echoes these points, stating that biologics *"…have been revolutionary in changing the way this disease is treated".* It is also noted in the ACD that patient experts have emphasised that biologics provided extensive benefits for people with RA and that the Committee themselves considers that *"biologics have significantly changed the management of rheumatoid arthritis"* In light of the evidence on the impact of biologics on patient outcomes, AbbVie believes that the Method Guide recommendations for discount rates other than the base case 3.5% are plausible and requests that the Committee take this into consideration at the next appraisal meeting.	
AbbVie	**1.4 Value of adalimumab patient support programs to patients and healthcare system** AbbVie would like to highlight the value of adalimumab beyond the drug, which has currently not been captured in either of the Assessment Group report and manufacturer submission. As stated in the AbbVie submission and subsequent consultations, AbbVie offers a free of cost patient support program (PSP) to adalimumab treated RA patients in the UK. The program includes elements such as homecare nurse visits, tailored self-management tools, telephone and online support for lifestyle and treatment advice. A recent study (NCT01383421) compared the clinical and functional outcome of 852 RA patients in the EU, Mexico, Puerto Rico and Australia who initiated adalimumab and used AbbVie's PSPs with patients on adalimumab who did not use these programs. The study reported significantly better ($p<0.05$) improvements in clinical outcomes (DAS28-CRP: −2.88 vs. −2.13; SDAI: −30.57 vs −21.65; and CDAI: −26.98 vs −20.75) and trends towards higher proportion of patients achieving HAQ MCID change (73.8% vs. 67.2%), from baseline at week 52 among moderate to severe RA patients in favour of patients who initiated adalimumab and used PSPs. Another study conducted in a US setting using 2,386 patients reported a 22% reduction in disease-related medical costs and 10% reduction in total healthcare costs associated with utilisation of PSP among adalimumab treated	Comment noted. The Committee made recommendations about the biological DMARDs are a group and heard from clinical and patient experts that they valued the availability of a range of biological DMARDs. The clinical experts also confirmed the Committee view that the evidence did not show differential effect between the biological DMARDs. The recommendations state that treatment should be started with the least expensive drug. The availability of patient support programmes could be considered when deciding to use the least costly drug.

	patients compared to non-PSP patients. Thus, the value of the AbbVie PSP has not been captured in the cost-effectiveness evaluations and as early studies have shown, improves patient outcomes and lowers the cost of treatment. For this reason AbbVie considers that ICERs for both severe and moderate RA for adalimumab may be underestimated in this appraisal and we request that the Committee take this into consideration at the next appraisal consultation meeting.	
AbbVie	**2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** Due to the reasons outlined in Section 1, AbbVie believes that the Committee may not reasonably have interpreted some elements of the clinical and cost-effectiveness evidence for biologics in this appraisal. We also question some of the statements and text within the ACD as detailed below. **2.1 Unclear justification for not considering the high responder subgroup in the moderate RA analyses** AbbVie notes that the Committee did not consider the sensitivity analyses for high responder patients in the moderate population plausible (Section 4.3.22), but do not offer an explanation for this in the ACD other than to state *"The Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group".* If, as the ACD states (Section 2.3.18), the Committee "*considered that such patients would be a subset of those currently having biological DMARDs and agreed it was appropriate to take this analysis into consideration when examining the most plausible ICER"* then this consideration should apply equally to the severe and moderate population. Without understanding the reasons why the Committee did not consider this subgroup relevant to the RA population, consultees and commentators cannot fully address this point and AbbVie therefore requests clarification on the reasons why the high responder subgroup in the moderate RA analysis was not considered plausible by the Committee.	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case ICER of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that the alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.
AbbVie	**2.2 Disconnect between efficacy/effectiveness of biologics and base case ICER in moderate RA compared to severe RA**	Comment noted. The probability of response is only one aspect of effectiveness included in the Assessment Group model. Effectiveness will also be

	As noted in Table 3 in the ACD, patients with moderate and severe RA will have the same probabilities of responding to biologic treatment based on the network meta-analysis. These findings are supported by result from various registries (including those of the BSR) which indicate toward similar or better clinical benefits of initiating biologics in moderate disease activity compared to severe disease activity state On this basis it is difficult to understand how the Committee could reasonably interpret the base case ICER for moderate RA to be the most likely ICER when it is £10,000/QALY higher than the severe population. In contrast, when comparing the ICERs in the scenarios for the high responder subgroup one can see that they are very close: £25,300/QALY and £28,500/QALY. Similarly, in AbbVie's own submission, the difference in ICERs between moderate and severe RA patients were £2,000/QALY. As there seems to be a disconnect between the efficacy of biologics (same efficacy) and the base case ICERs (£10,000/QALYdifference), AbbVie request that the Committee reconsider that the base case ICER for moderate RA is the most likely ICER for this group of patients. The more likely ICERs would be that of the high responder subgroups.	determined by patient baseline characteristics, change in HAQ on starting treatment and HAQ progression rates. These factors would also contribute to the differing ICERs for moderate and severe active disease.
AbbVie	**2.3 Query on the annual cost of infliximab, biosmilar infliximab and tocilizumab in the ACD** AbbVie has some concern regarding the ACD text in bold in the sections outlined below: *Section 3.10* *… The net price of infliximab is £419.62 per 100-mg vial (BNF, April 2015). Assuming a weight per person of 70 kg**, no vial wastage** and 3 initial doses followed by treatment every 8 weeks, the cost in the first year is £7049.62, and then £5727.81 per year...* *Section 3.12* *The net price of infliximab biosimilars is £377.66 per 100-mg vial 3.12(information provided by the companies). Assuming a weight per person of 70 kg, **no vial wastage**, and 3 initial doses in the first year*	Comment noted. The wording of the sections mentioned in your comment has been amended and the costs calculated assuming vial wastage were included in the FAD.

	followed by treatment every 8 weeks, the cost in the first year is £6344.69, and then £5155.06 per year… *Section 3.31* *.. The net price of tocilizumab is £102.40 per 4-ml (80-mg) vial, £256.00 per 10-ml (200-mg) vial, or £512.00 per 20-ml (400-mg) vial (BNF, April 2015). Assuming a weight per person of 70 kg, **no vial wastage**, and 13 doses per year, the annual cost (without the patient access scheme) of tocilizumab is £9318.40* AbbVie queries whether it is appropriate to base the annual cost of infliximab, biosimilar infliximab and tocilizumab on the assumption that no vial wastage will take place. This is not an assumption that was made by any of the manufacturers or the Assessment Group in their cost-effectiveness calculations but most importantly, AbbVie understands that this is not commonly done in clinical practice and that it may not be considered acceptable due to the risk of contamination when keeping opened vials and sharing it between patients. Additionally, the Summaries of Product Characteristics (SPC) for Inflectra and Remsima state: "Any unused portion of the infusion solution should not be stored for reuse". Similarly, for Remicade the SPC states "Do not store any unused portion of the infusion solution for reuse" and for tocilizumab "RoActemra is for single-use only". AbbVie therefore requests that these sections be amended to reflect the annual cost based on no vial sharing, as in its current format it may be interpreted by the reader that the cost-effectiveness decision was made based on the cost of vial sharing.	
AbbVie	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Due to the points discussed previously AbbVie does not believe that for patients with **moderate** RA, the provisional recommendations are sound or a suitable basis for guidance to the NHS. When first introduced, biologic therapies offered a step change therapy for people who have failed conventional therapy in moderate to severe RA. Indeed, it is now widely accepted that patients with persistent moderate and severe RA despite treatment with cDMARDs should be escalated to biologic therapy and this is reflected in treatment guidelines around the world from	The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case ICER of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include

	organisations such as the BSR, EULAR, and the American College of Rheumatology. We also note the Committee considered biologics and innovative class of drugs. Not surprisingly therefore, **the use of these agents is standard of care across Europe and is also widely reimbursed in major European countries**. However, there are some striking and disconcerting findings in a cross-sectional study exploring access to biologics for RA patients among 46 European countries. Crucially, among European countries where there is reimbursement for biologics their finding was that the UK was only 1 of 8 countries in Europe requiring a DAS score >5.1, while 18 had no DAS requirements or permitted biologics in moderate and severe disease, while 10 countries permitted biologics with a cut-off between 3.2-5.1. When exploring a composite score for clinical eligibility criteria to initiate a biologic, 4 countries had the maximum eligibility score (5 - most liberal), 12 countries had score 3 or 4 and 20 scored between 0 and 2 (most restricted). Countries from Eastern Europe and Former Soviet Union were more likely to be classified in the more restricted scores. It is notable that the UK was scored a 1 representing highly restricted access to biologics, and was the only western European country to be classified as having poor access. The authors also note that stricter clinical eligibility criteria seem to also be associated not only with lower uptake of biologics, but also with higher disease activity, thus suggesting that principles of equitable heath care systems might be undermined within Europe. Additionally, AbbVie considers it is important for **patients with moderately active disease** to have the opportunity to receive biologics as those who fail biologic therapy **will still be left with the prospect of poor quality of life and/or becoming disabled as result of staying on failing treatment**. As emphasised in the BSR Guidelines patients on aggressive cDMARD therapy including steroids may still have a DAS28<5.1 and yet still have very active disabling disease. Some of these patients may be corticosteroid dependent despite combinations of cDMARDs. Furthermore, corticosteroid use may reduce the DAS28<5.1, yet still not control disease satisfactorily. The NICE RA Management Guidelines recommend that attempts should be made to remove corticosteroids whenever possible, including the tactic of using biological drugs. It would be unethical to expect clinicians to withdraw therapies in these patients in an attempt to achieve the NICE criteria for access to biologic therapies as it would in effect precipitate a flare. A possible solution to the concerns around the cost effectiveness of expanding	moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that the alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.

	access for biologics to patients with moderate disease activity would be to **define a subgroup at highest risk of poor outcome**. Factors associated with poor prognosis do not simply include a high DAS28 (a cut-off noted as arbitrary in the ACD), but also include other factors such as high baseline HAQ score, seropositivity, baseline radiographic damage and swollen joints. This is based on the EULAR recommendations which refer to earlier use of biologics in the presence of prognostically unfavourable factors such as early joint damage and rheumatoid factor (RF)/anti-citrullinated protein antibody (ACPA) positivity, whilst the ACR guidelines defines poor prognostic features as functional limitation, extra-articular disease, positive RF/ACPA and bony erosions by radiograph.In the BSR Guidelines on Eligibility for First Biological Therapy there is a requirement for demonstration of at least three tender and swollen joints. In their study using the ERAN database, Kiely et al. found that patients with a DAS of 4.2-5.1 had a worse outcome, and both HAQ and employment outcome were significantly worse, than those with a DAS 3.2-4.1, suggesting that this group may stand to gain the most from anti-TNF therapies. The possibility of a subgroup of moderate patients for whom biologics are most appropriate is an area we hope the Committee can further explore with the clinical experts at the next appraisal meeting. To conclude, on the basis that AbbVie believes that patients in the UK should receive the same standard of care as in the rest of Europe for a potentially disabling disease, we would urge the Committee to give due consideration to extending the availability of biologics to patients with moderate RA. *References were provided but not reproduced here.*	
AbbVie	**4. Are there any aspects of the recommendations that need particular consideration to ensure NICE avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** AbbVie has no comments on this point.	Comment noted, no actions required.
Bristol Myers-Squibb	**Comments on the ACD** We welcome the draft guidance recommending biologic DMARDs in combination with methotrexate as an option for the treatment of patients with severe rheumatoid arthritis (RA). We acknowledge that the majority of patients with RA currently receiving a	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further

	biologic DMARD to manage their condition (severe disease DAS 28 >5.1) will be able to continue to receive appropriate treatment. We also welcome the further clarity of the continuation and stopping rules based on EULAR response, which we believe is consistent with clinical practice in England and Wales. Although the ACD recommends that treatment should be started with the least expensive drug (taking into account administration costs, dose needed and product price per dose),.we would emphasise that the choice of drug should be based on a comprehensive assessment of the patient's disease severity, clinical course as well as other clinical and individual needs. With respect to the analysis of patients with the fastest Health Assessment Questionnaire (HAQ) progression, we are unclear about the Committee's rationale that this dataset is not as applicable to the moderate active group as to the severe active group. ERAS, the dataset on which this analysis was based, contains data on both moderate and severe patients; indeed the mean DAS score at baseline is 4.501 (DSU report, Section 4.1.1). The DSU report does not suggest that patients with moderate and severe RA have different probabilities of belonging to the latent dropout classes, so we believe that the analysis is equally as applicable to patients with moderate RA. Furthermore, the clinical experts who attended the second Committee meeting on 21st May 2015 stated that the initial DAS score does not define patients who progress fastest, and that the Committee did not feel sufficient evidence was presented regarding the characteristics of these patients (ACD, 4.3.18). On the basis of this evidence, we believe there is insufficient evidence to define patients with the fastest HAQ progression by a DAS score >5.1. The Committee noted the clinical interest in the use of biological DMARDs in people with moderate active disease (ACD section 4.3.5); plus guidelines from the British Society of Rheumatology (BSR) make this recommendation. Access to biologic DMARDs for patients with moderate disease could prevent the joint damage and impairment resulting from RA and increase patients' productivity. We would encourage the Committee to consult further on its proposed recommendation not to recommend the biologic DMARDs in fast progressing patients with moderate disease, and to reconsider the ERAS analysis as well as explore additional data sources in this patient subgroup. Specifically, we believe participants in the appraisal should be invited to submit additional data for fast progressing patients with moderate disease, as, ultimately, we believe	details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case estimate of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that the alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.

	the evidence could lead to NICE recommending the use of biologics in patients with moderate RA. *References were provided but not repeated here.*	
Bristol Myers-Squibb	**Comments on the updated final scope** We were surprised that the decision was taken to include biosimilars in the scope of the MTA without any consultation. In addition, we were notified of the change to the scope on 13th April 2015, which we believe was an inappropriately late stage in the process. Adding new technologies mid-way through an appraisal is a substantial deviation from NICE's standard process for MTAs, and this change to the Final Scope had implications for all manufacturers involved. We acknowledge that the Committee 'concluded that the availability of biosimilar treatments was not currently a key driver of cost-effectiveness' in this specific appraisal (ACD section 4.3.10); however we are concerned that this sets a precedent, which could be followed by similar 'late inclusion' of biosimilars into subsequent MTAs with limited (or no) timely consultation. This could lead to biosimilar medicines being appraised by NICE without the full and balanced consideration of all available evidence, which is not in line with NICEs Methods of Technology Appraisal. Finally we confirm that we have not identified any factual inaccuracies in the ACD or the economic model. We would be grateful if you would consider the points that we make in this response prior to the meeting of the Appraisal Committee on Wednesday 22nd July 2015.	Comment noted. The infliximab biosimilar products were included in the appraisal in accordance with the NICE biosimilars position statement: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/biosimilars-statement.pdf The inclusion of biosimilar products in the appraisal did not affect the recommendations of the Committee.
UCB Pharma	**Has all the relevant evidence been taken into account?** **Exclusion of UCB key registration trials** UCB welcomes the acknowledgement that the Committee gives in the ACD to the AG's sensitivity analysis where a wider and complete network of trials was employed, including those trials with a small proportion of patients who had prior biologics, which reflects the discussions that took place during the last Committee meeting. **UCB is pleased that the ACR responses from this analysis of the**	Thank you for your comment. The exclusion and inclusion of clinical trial data in the network meta-analysis by the Assessment Group was discussed by the Committee. It noted that that the RAPID trials had been included in both clinical and cost-effectiveness sensitivity analyses, so that the effect on the ICERs of the inclusion and exclusion criteria of the systematic review could be seen. The Assessment Group's analyses demonstrated that the economic model was not very sensitive to the estimates of probability of initial response and this did not affect the Committee's recommendations. For further

	complete network are presented in Table 4, but are concerned that the EULAR responses presented in Table 3 (p.21) in the ACD remain those from the AG's primary analysis where the main registration Phase III trials for certolizumab pegol (CZP) (the RAPID studies) were excluded. Currently, the only CZP trial that the Assessment Group includes in their primary analysis of the moderate to severe population (Populations 2 and 3 combined) is the CERTAIN study, conducted in low to moderate RA patients only (see in Appendix for an overview of the CZP studies included and excluded in the AG network meta-analysis). The inclusion of patients with prior experience of biologics would have minimal impact on the results. Post-hoc analyses were conducted on the RAPID 1 and 2 studies, by excluding those subjects with prior biologic exposure (3.5% (34/982) and 4.8% (30/619) from the ITT, respectively). The exclusion of the small subset of patients [redacted] with prior biologic exposure had no impact on the main results or primary conclusions of the studies in terms of ACR20 at Week 24 (Figure 1). Similarly, the conclusions were maintained for ACR50/70 and EULAR responses (Appendix). The consideration of the CERTAIN trial (conducted in low to moderate RA patients) as the only relevant evidence of the efficacy for CZP in the primary AG analysis in the combined moderate and severe RA populations, penalizes CZP and biases the results to be more in favour of the other biologics over CZP. UCB is concerned that the current main AG analysis therefore provides a misleading conclusion to health care professionals, as it does not accurately reflect the evidence base for CZP in severe RA patients. The two registration RAPID studies for CZP, which have been excluded from the AG's primary analysis, represent a very large clinical program, with over 1,275 RA patients in the active arms, and have supported the current CZP license in Europe. These trials have also been acknowledged and accepted in the previous NICE positive recommendation of CZP (NICE TA186, 2010). **UCB re-emphasise that the RAPID studies are appropriate and within scope for inclusion and request that they are considered part of the main analysis and that the EULAR response results from this wider complete network is presented within the base case analysis in the final guidance document.** It is important that all the clinical evidence presented in the final guidance document includes the CZP pivotal registration studies to accurately reflect its proven efficacy within its EU license and in the population under	discussion please see section 4.95 of the FAD.

	evaluation in this MTA. *Figure1 has been received but not reproduced in the table.* *References were provided but not repeated here.* **RAPID2 EULAR response data** The RAPID2 study was not included in the AG's wider network for EULAR response as this data is not published and was not provided in our original submission. Please find below in Table 1 the EULAR response data for the intention-to-treat population of RAPID2. If possible, we would ask that the AG's sensitivity analysis on the wider network for EULAR response be updated to include this additional data. *Table 1 has been received but not reproduced in the table* **Exclusion of certolizumab pegol monotherapy data** UCB would like to raise the point that the evidence for CZP in monotherapy has been excluded from the Assessment Group's NMA despite the approved EU license and supportive evidence (the FAST4WARD and HIKARI studies). FAST4WARD was originally not considered by the AG due to the 4-weekly dosing that was used in this trial (see Section 1.1 Table 2 in the Appendix). UCB would like to note that the 4-weekly dosing was included within the CZP SmPC as of November 2013. The FAST4WARD data for ACR20/50/70 response, which was presented in the UCB original submission, is shown again in the Appendix of this document; the EULAR response data is not available for this trial. For the HIKARI study, we provided the ACR20 results at week 12 for the monotherapy subgroup within our original submission, and this is also presented again in the Appendix. We would therefore ask that the FAST4WARD and HIKARI studies are considered as relevant evidence for CZP in monotherapy and that the following sections of the ACD are updated: • Table 3, page 21, which currently does not include CZP monotherapy • Section 4.1.10 on the assessment group's wider network of trials it is	Comment noted. These data were not included in the Assessment Group's analyses. However the Committee was aware of these data and the recommendations include certolizumab pegol monotherapy.

	stated that: "This allowed the inclusion of all biological treatments, with the exception of certolizumab pegol monotherapy." Given that the current decision to not recommend biologic monotherapy leaves the patient group who cannot take methotrexate with very few therapeutic options (see section of the present response), the Committee should ensure that they are appraising all the available evidence for the final guidance. *References were provided but not repeated here.*	
UCB Pharma	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **ICER for monotherapy in moderate population** Section 4.2.35 of the ACD summarises the results for biological DMARD monotherapy for moderate active rheumatoid arthritis previously treated with methotrexate (MTX) and indicates that results for this population were provided by AbbVie and UCB. Section 4.2.18 also mentions that UCB provided analysis of CZP monotherapy in the moderate population. We would like to clarify that UCB did not conduct any cost-effectiveness analysis of biologic monotherapies in moderate RA patients previously treated with MTX. The following inaccuracies have therefore been identified: • Section 4.2.18 incorrectly suggest that UCB submitted a moderate monotherapy model. We ask that this section is re-phrased to: "UCB submitted analyses for the severe active (as monotherapy and with methotrexate) and moderate active populations (with methotrexate only) who had previously had methotrexate." • Section 4.2.35: the ICER of £49,226 reported in this section was for CZP + MTX versus conventional DMARDs in the moderate population, not for CZP monotherapy as the text implies. This reference to the UCB submission should be removed completely from this section. • Section 4.2.27 reports an ICER of £47,821 for CZP in combination with MTX compared to conventional DMARDs. We would like to clarify that the ICER of £47,821 was for CZP + cDMARDs, and not CZP + MTX (which is £49,226 as reported above). The ICER reported in Section 4.2.27 should therefore be changed to £49,226 per QALY.	Thank you for your comment. The relevant sections of the FAD have been corrected.

	UCB requests that sections 4.2.17, 4.2.18 and 4.2.35 are revised to accurately reflect the results submitted by UCB.	
UCB Pharma	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** **Moderate RA population** Following the draft guidance in the ACD, access to biologics in the UK is still restricted to a much greater extent than seen in the rest of Europe, meaning that the UK will lag behind its European counterparts in terms of the quality of care that patients with RA receive. The latest BSR biologics guidelines recommend that biologics can be initiated for moderate patients with a DAS-28 >3.2, and they justify this extensively by citing evidence from the ERAN and ERAS databases that show that the majority of RA patients with a DAS-28 of 3.2-5.1 at 3 years have only marginally better functional, radiological and orthopaedic outcomes at 5 years when compared with those with a DAS-28 > 5.1, indicating that the burden of moderate RA is similar to that of severe RA.5 As indicated in the UCB original submission, it is recognised that there is a substantial burden (including pain, fatigue and loss of physical function) associated with patients exhibiting moderate disease activity. Furthermore, it is well established that in patients with moderate disease activity, radiographic progression (evidence of joint damage visible and measurable via X-ray) can continue, which can lead to permanent loss of function and disability. This can have a significant impact on patients' ability to work and therefore moderate RA imposes a substantial productivity cost to society. The importance of treating patients with moderate disease activity is well acknowledged, and the efficacy of anti-TNFs in patients with moderate disease activity has been demonstrated in both clinical trials and registries. For example, Hyrich et al. (2009) demonstrated that treatment of patients with moderate disease activity with anti-TNF therapy confers substantial benefits based on an analysis of the British Society for Rheumatology Biologics Registry (BSRBR). Additionally, the open-label run-in PRESERVE trial of etanercept and the randomised controlled CERTAIN trial of CZP show clear benefits of anti-TNF use in a moderate disease activity population. Although treatment with biologics may not be cost-effective in the overall moderate disease population, the AG analysis has shown that there is a sub-set of the moderate patients who have the greatest HAQ progression for which biologic therapy is cost-effective (ICER = £28,500 per QALY). The single statement in Section 4.3.22 that "the Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group", does not give any explanation or	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case estimate of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that the alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.

	justification for why the Committee came to this conclusion. UCB would like to understand further why the Committee has come to a different decision for moderate patients than for severe patients who have the greatest HAQ progression.	
UCB Pharma	**Recommendations on monotherapy** UCB are concerned that the Committee came to the conclusion that they were "not persuaded that biological DMARDs were a cost-effective use of NHS resources when used as monotherapy" (Section 4.3.23), whereas previously NICE recommended specific biologics, including certolizumab pegol as monotherapies, when continuing methotrexate is not appropriate (TA1862, TA1306). UCB would like to highlight that this leaves a significant number of patients who are intolerant or contraindicated to methotrexate without access to biologic therapy. These patients have few other options and therefore would continue to suffer with high disease activity, poor functioning and low quality of life. Disease severity and disability are also linked to premature mortality in patients with RA.7 Similarly to the overall severe RA population, there will be those patients who cannot take methotrexate who are at high risk of HAQ progression and for whom biologic therapy is cost-effective. UCB hopes that the Committee will reconsider their decision over monotherapy, particularly in light of the additional evidence that should now be taken into consideration in the analysis (see Section 1.3) and in such a case where there is no alternative therapy that the Committee are willing to accept a higher degree of uncertainty around the ICERs.	Comment noted. As a result of consultation in an exploratory analysis the Assessment Group has calculated the ICER for the subgroup of patients with severe active rheumatoid arthritis, who cannot take methotrexate and has the greatest HAQ progression. This scenario resulted in an ICER of £29,000 per QALY gained. For further discussions, please see section 4.84 of the FAD. The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.
UCB Pharma	**Position on biosimilars** UCB acknowledge NICE's position on appraising biosimilars through multiple technology appraisals. We recognise that the inclusion of the infliximab biosimilars was not in the original scope but understand the reasons for their inclusion at this later stage. We would like to highlight that biosimilars should not be considered interchangeable with their originator brands, as supported by the MHRA biosimilar guidelines,8 and hope that any NICE guidance reflects this.	Comment noted, no actions required.
Roche	Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the Rheumatoid Arthritis (RA) Appraisal. We are pleased that the Committee has recognised the important place that	Comment noted. The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy

	biologics have in the treatment of RA. We remain unconvinced that the Assessment Group (AG) have adequately modelled the patient population which is being assessed within the scope of the Appraisal. In our response to the DSU report in April 2015, we highlighted that there were significant differences between the patient population being assessed and those used to evaluate the long term HAQ progression rate. We strongly believe that the Committee is making a recommendation on evidence which is not reflective of the RA population considered in this Appraisal. We are gravely concerned that those patients who are unable to tolerate MTX will have their access to proven and effective treatments withdrawn. The Committee's draft decision would result in the removal of access for a well-defined group of patients with high unmet need, on the basis of factors that are outside of the scope of this appraisal (i.e. second-line treatment options), despite RoActemra® (tocilizumab) having demonstrated comparable efficacy with or without MTX at the same cost. A number of errors and oversights have also been identified, which we believe have not allowed the Committee to generate recommendations based on a complete view of the relevant information. The following appendix provides further detail on our concerns with the evidence supporting the ACD and suggested approaches to allow the Committee to make a more considered recommendation.	and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.
Roche	**<u>Significant unmet need in UK patients unable to tolerate MTX</u>** We would like to highlight to the Committee the significant unmet need which exists for a clinically distinct group of RA patients, those who are unable to tolerate or are contra-indicated MTX. The Committee's decision as it stands will remove all biologic treatments for this group of patients, increasing the risk of severe disability and disease progression. Not all RA patients have the option to use MTX with their biologic due to a number of contra-indications, including (but not limited to) liver or lung disease [Methotrexate Summary of Product Characteristics July 2014]. Furthermore, of those that begin treatment with MTX, a significant proportion (17%) will stop treatment within the first 6 months [Lie et al, 2010]. A large body of evidence suggests that between 6-21% of patients will become intolerant to MTX [Calasan et al, 2013; Fitzpatrick et al, 2012, Hoekstra et al, 2003; Vertappen et	Comment noted. As a result of consultation in a exploratory analysis the Assessment Group has calculated the ICER for the subgroup of patients with severe active rheumatoid arthritis, who cannot take methotrexate and has the greatest HAQ progression. This scenario resulted in an ICER of £29,000 per QALY gained. The Committee also noted comments from consultation that rituximab may be used in clinical practice as monotherapy, even though it is not licensed. For further discussions, please see section 4.112 of the FAD. The Committee discussed the use of biological

	al, 2010; Jacobs et al, 2012; Schabel et al, 1996; Kremer et al, 1992; Lie et al, 2010[Error! Bookmark not defined.]. MTX intolerance can stem from a number of different adverse events, but most commonly cited are those related to gastrointestinal effects. However, just as debilitating, but less well known, are the behavioural symptoms which includes restlessness, irritability and refusal of MTX which develop in response to MTX-induced gastrointestinal symptoms and anticipation thereof [Calasan et al; 2013] The current draft recommendation – which will remove patient access to a biologic when administered as monotherapy – will have a significant clinical impact on this group of patients, and will create a significant unmet need. **<u>MabThera® as a second-line treatment</u>** 1. The AG report states that RoActemra® (tocilizumab) is less cost-effective in monotherapy than if received as part of combination therapy. This lacks face validity, as RoActemra has comparable outcomes with or without the use of MTX [ACT-RAY Study, Dougados et al, 2012]. The ACT-RAY study demonstrated that after 24 weeks of treatment in patients who had previous exposure to MTX, there was no statistically significant difference in clinical or radiographic outcomes, between patients treated with RoActemra monotherapy and patients treated with RoActemra + MTX combination therapy. The data demonstrate that RoActemra efficacy is not compromised for patients who require biologic monotherapy and who are intolerant to/cannot continue to take MTX. The AG correctly identified the main driver for the difference in the ICERs to be a result of the cost of later line therapies, and not the efficacy of the interventions under assessment in this Appraisal (as highlighted in Figure 1). *Figure 1 has been received but not reproduced in the table.* The analyses conducted by the AG did not consider the use of MabThera® (rituximab) as a monotherapy agent following a patient's progression on one of the interventions considered in the scope. Although not licensed, MabThera is routinely used in the UK as monotherapy treatment, as supported by numerous local treatment protocols [Pan Mersey; Guys and St Thomas'; Lancashire; Manchester].	DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.

	We have provided a recent real world study, which evaluated the outcomes of patients treated with MabThera in Germany [Wendler et al, 2014]. The efficacy of MabThera as a monotherapy treatment is comparable to that when used as part of combination therapy. Therefore, when MabThera is included in both treatment lines as a second line therapy, the ICER for RoActemra will be similar in monotherapy and combination treatment. We would be disappointed if the Committee made the decision to not recommend biologics in those RA patients who cannot receive MTX, based on an analysis which does not reflect UK treatment practice and falls outside the scope of this Appraisal. While MabThera does not have a licence for use as a monotherapy treatment in RA, it is common practice in the UK for it to be used in this setting, as supported by numerous local protocols [Pan Mersey; Guys and St Thomas'; Lancashire; Manchester]. If the AG were to reflect routine UK clinical practice for the treatment of RA patients intolerant or contra-indicated to MTX, the clinical data for RoActemra and MabThera would support a similar cost-effectiveness result in the AG analyses, irrespective of the use of MTX. *References were provided but not repeated here.*	
Roche	**<u>Factual error and oversight in the AG modelling</u>** **i. Applicability of 'fast progressing' patients in the monotherapy** The Committee considered at the last Appraisal Meeting a subgroup of patients who are deemed to have 'faster progressing' RA. The AG completed the analysis for patients with 'faster progressing' RA when biologics are prescribed in combination with MTX. We believe the Committee has overlooked the relevance of this subgroup in those patients who cannot tolerate MTX. We consulted an expert clinical specialist, who explained that the baseline progression rate would be the same whether a patient can or cannot tolerate MTX. Therefore, it would be appropriate for the AG to perform a similar 'fast progressing' analysis for monotherapy patients. The AG did not present this analysis to the Committee, and we believe this is critically important in order for a fair and equitable decision to be made. **ii. Monotherapy analysis in the economic model** In replicating the results of the AG, we believe the treatment costs of MTX	Comment noted. As a result of consultation in a exploratory analysis the Assessment Group has calculated the ICER for the subgroup of patients with severe active rheumatoid arthritis, who cannot take methotrexate and has the greatest HAQ progression. This scenario resulted in an ICER of £29,000 per QALY gained. Comment noted. The cost calculations in the model were discussed at the Committee meeting. The Committee heard from the Assessment Group that the model isn't sensitive to small changes in drug or

	have been erroneously included in the modelling of the monotherapy treatment arm. Based on the terms of the confidentiality agreement under which the economic model was distributed, we have not rerun the model, but believe the impact of replacing the cost of MTX with sulfasalazine would slightly improve the ICER for all treatments. *References were provided but not repeated here.*	administration costs. This is shown in the sensitivity analyses using alternative drug acquisition costs. The main drivers of the cost effectiveness were the HAQ progression rates, HAQ utility mapping function and discounting rates.
Arthritis Care	The main recommendation of the ACD supports the current position that these drugs remain available only to those most severely affected. While Arthritis Care welcomes the committee having taken into account the additional evidence to ensure the continuation of these drugs, we believe an opportunity has been missed to extend their use for people with moderate disease who experience the same painful and debilitating symptoms of RA. This position means that the UK remains an outlier in Western Europe where there is greater access to these drugs. We believe that there is no economic or clinical justification for this to continue as the NICE ACD clearly shows that the formula used to demonstrate cost-effectiveness for the NHS gives very similar results for both severe and moderate patient groups. We believe that it is false economy not to treat patients with moderate disease with biologic therapy when standard DMARDS fail as these people will be higher users of healthcare resources. These patients will require more attendance to primary and secondary care, and are more likely to develop co-morbidities such as osteoporosis, heart disease and have more surgery. They are also much more likely to lose their jobs causing financial hardship and some may also face earlier mortality, as uncontrolled disease decreases life-span by 6 - 10 years. The personal costs to the individual, the NHS, the impact on the rest of their family and the direct cost to the exchequer in lost productivity and benefits claims is considerable. These treatments could restore quality of life and enable people to remain in work, help look after their families and contribute fully to society.	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case estimate of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that the alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.
National Rheumatoid Arthritis Society	Thank you for the opportunity to comment on the Appraisal Consultation Document relating to the above MTA. We welcome the publication of the draft MTA ACD provisionally recommending access to biologic medicines for patients living with severe RA, but have some real concerns which we outline below which align with those expressed by the	Comment noted, no actions required.

	BSR: • Ongoing access to bDMARDS in patients with severe, active RA • Removal of access to those patients who are intolerant to or are contra/indicated for MTX, who would previously have had access to mono-therapy bDMARDs • Access for people with moderate disease but who have poor prognosis **Ongoing access for patients with severe, active RA** We are relieved that patients with severe active disease will have on-going access to these drugs which are so life-changing for many. We also understand in a cash-strapped NHS where rationing has to happen that only patients who are at greatest risk of poor prognosis and worsening disease should receive these therapies. We agree with the BSR clinical experts that active synovitis despite combination therapy and tight control is an indicator of poor outcomes and that this ACD does represent a more stringent threshold than previously, but one which aligns with current best practice and guidelines.	
National Rheumatoid Arthritis Society	**Access to bDMARDs for patients with intolerance and/or contra-indications to MTX** We are, however, dismayed to see that these two small but important groups of patients are being denied access to bDMARD monotherapy. This is in stark contrast to previous NICE TAs, flies in the face of current best practice which has been established for many years and we believe would be an unfair and retro-grade step for these patients who would be singularly disadvantaged and would have to live with progressive disease, increasing disability, pain and suffering or have to live with debilitating side effects which can all too easily lead to job loss, depression and very diminished quality of life. We speak to people who are intolerant to MTX and call our helpline and know how disruptive and unpleasant side effects can be and it is, we believe, unreasonable and unfair to exclude this group and those who are already disadvantaged by being contra-indicated in some way. We completely agree with the BSR's comments on patients wishing to conceive. We would strongly urge the Committee to re-consider their initial recommendations in regard to the above groups and allow monotherapy bDMARD prescription for those who are either intolerant to or have a contra-indication to methotrexate.	The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.
National Rheumatoid Arthritis Society	**Access for people with moderate disease/poor prognosis** We fully support the BSR position in regard to this group. As the ICER from the exploratory analysis for the moderate group falls within the cost effective range set by NICE, we would request that NICE re-consider their initial recommendations not to extend the guidance to this group and in particular	Comment noted. The Committee did not consider that the Assessment Group exploratory analyses of the fastest HAQ progression with the ICERs of £25,300 and £28,500 could be used as the basis for decision making, because these were not based on

	would endorse the data findings presented by the BSR, which evidence that those with moderate disease, but who have a rapidly progressing course of disease, do constitute a major clinical problem and should be eligible for bDMARDs if they fail combination therapy. We went back to the data we presented for the meeting on 21st May, gathered from our survey and extrapolated those patients who were on cDMARDs and do not meet the current eligibility criteria for biologic treatment, so have a DAS of less than 5.1. The following data reinforces the BSR position we believe and demonstrates the importance of treating this group of patients who are likely to continue to be expensive to treat if they remain unable to access the most appropriate biologic therapy to gain adequate control of their disease: 288 patients met the criteria for currently being on cDMARDs and not therefore meeting current criteria for biologic access. Of the total, 20 were male and 268 female. Out of the 288, 60% were in the age range 35-54, so in the prime of their working life, bringing up families. We asked how long people had been diagnosed and over 55% had been diagnosed within the last 5 years. *Figure has been received but not reproduced in the table.* We wanted to know how many were in employment and their employment status and the following two graphs illustrate this. *Figure has been received but not reproduced in the table.* We asked of the 45.1% of participants who were not working, the reason that they were not employed and found, shockingly, that 63% were not employed due to their RA with the breakdown as follows: 33.85% were currently unable to work due to their RA 22.31% had retired due to their RA 6.92% had never been able to work due to their RA *Figure has been received but not reproduced in the table.* We then asked about pain and fatigue impact during the last 6 months, using a visual analogue scale from 0-10 where 0 is not severe at all and 10 is very severe. In the case of pain, the average score for the 287 people who answered the question was 6.85 and 7.67 in respect of fatigue, both of which are relatively high, and are very debilitating symptoms to have to live with on a regular basis.	any pre-specified patient characteristics. For further details please see section 4.107 of the FAD. The Committee was not persuaded that the analysis of fastest HAQ progression was as applicable to the moderate active group as for the severe active group. For the severe active group, the Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the Assessment Group's base-case estimate of £41,600 per QALY gained for the severe active population may be overestimated. However, for the population with moderate active rheumatoid arthritis the Committee was not persuaded that expanding treatment to include moderate active disease measured by DAS would target patients whose disease was progressing rapidly, nor was it persuaded that the alternative criteria proposed to identify patients with the fastest HAQ progression could currently be used for decision making. For further details please see section 4.111 of the FAD.

	"I have tried 5 DMARDs and getting increasingly frustrated at the failures. I am not sure if biologics are the way forward for me but if the choice was not there I would be devastated". "I'm very worried. At the moment I feel that biologics are future treatment options for when I need them. If that option were not available to me, it would be like someone telling me that I will be in pain and tired for the rest of my life and will have to try and survive on ever increasing doses of strong, addictive pain relief. I would not want to live like that with no hope of an effective treatment." We also asked participants a question relating to identifying which of the following situations applies to them and these answers give a clear picture as to the serious way in which RA impacts on this group of patients: Out of 284 who answered the questions: o >60% said their disease is not well enough controlled to enable them to continue to do valued day to day activities o Just under 60% said their disease is not well enough controlled and this is affecting their confidence and independence o Just under 25% said their disease is not well enough controlled and is affecting their ability to remain in their current job o Just under 10% said their disease is not well enough controlled and as a result they have lost their job "I would be terrified. I am 30 years old, struggle to walk, to cook, have had to downgrade my job and lost a lot of income. I hope I will be put onto biologics as soon as I am eligible, and really really hope they work." I hope that the above results from our recent survey and the attached case studies will give you and the committee an insight into the plight of those people who fall into the 'moderate' disease category, yet who have the poor prognostic markers and really need access to biologics in line with the rest of Western Europe. We appreciate that we must be careful with precious NHS resources and cannot necessarily recommend that biologics be made accessible to all patients in the DAS 3.2-5.1 'moderate' category. We therefore confirm that we concur with the BSR proposal regarding patients in this group who have strong predictors of progressive disease as evidenced by active synovitis, persistently elevated inflammatory markers, erosions on x-ray and a positive ACPA. We strongly believe that left untreated, these patients will be more expensive to the NHS in the long run, not only in regard to treatment for their RA, including	

	surgery and in-patient spells, but through greater co-morbidity including mental health issues such as depression, anxiety and of course to wider society through loss of work and financial independence. In conclusion, we would like to see access to bDMARDs for those who cannot tolerate or are contra-indicated for MTX for the reasons both we and the BSR have identified and would urge the committee to consider access for those with moderate disease but restricting this to those who can be identified as having a rapidly progressive course. We believe that we are recommending actions which are fair, reasonable and whilst not fully aligning England and Wales with the level of access which those patients in the rest of Western Europe get to biologic therapies, go a crucial step further than currently exists and that this is fully justified in both humanitarian and economic terms.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
Roche	Current recommendations underestimate the need for biologic monotherapy and considered biologic monotherapy as an option rather than necessity. A significant number of patients with RA have contraindication to methotrexate such as liver or lung disease. Many more developed side effects such as neutropenia so methotrexate had to be withdrawn. Large longitudinal cohort study involving 1218 patients with RA and 430 patients with PsA found that 17% of patients discontinued methotrexate within the first 6 months of initiation of therapy (Lie E et al Ann Rheum Dis 2010;69:671-676). The main reason for discontinuation was adverse events (47%). Mortality in patient who could not take methotrexate was substantially higher more than twice when compared with other non-biologic conventional DMARDs such as sulfasalazine (Choi HK et al Lancet 2002;359:1173-7). Use and duration of methotrexate reduced mortality (Wasko MC et al. Arthritis Rheum. 2013;65:334-42). Importantly all the evidence of supporting the of combination conventional non-biologic DMARD therapy includes methotrexate. Hence for patients who have contraindication to methotrexate or were intolerant of methotrexate, combination conventional DMARDs is not an option. Lastly, the model assumes HAQ progression in control arm for biologic monotherapy therapy is the same as biologic in combination with methotrexate. This is inappropriate since most of these patients will be taking methotrexate.	The Committee discussed the use of biological DMARD monotherapy. It understood that the difference in the ICERs between monotherapy and combination therapy were mainly driven by the costs of later treatments rather than the costs or benefits of the first biological DMARD. It concluded that the minority of the people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe active disease, as far as possible. The Committee recommended biological DMARD monotherapy as a cost effective use of NHS resources. For further details please see section 4.112 of the FAD.

Nominating organisation	Comment [sic]	Response
	In addition, there are a number of factual errors: Page 16. Section 4.1.1 TACIT was a trial comparing TNF-alpha inhibitor against a combination of conventional DMARDs	Thank you for your comment, the relevant section of the FAD has been amended.
	Page 17, 4.1.3 Table 3 is incorrect for AMPLE study which is a study comparing methotrexate plus adalimumab versus methotrexate plus subcutaneous abatacept	Comment noted. The FAD has been amended to indicate subcutaneous abatacept.
	Section 6.77: If patient has a contraindication to methotrexate the option of DMARD combination or biologic combination with methotrexate does not exist.	Thank you for your comment, the relevant section of the FAD has been amended.

Comments received from commentators

Commentator	Comment [sic]	Response
Department of Health	No comment.	Comment noted, no actions required.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
None received			

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