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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

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 manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

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 may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
BMS & Otsuka Pharmaceuticals	Abatacept shows an innovative mode of action. It is a T-cell modulator that blocks the co-stimulation mechanism that activates T-cells, a pivotal step in the RA inflammatory cascade and subsequent joint destruction. This upstream modulation of T-cells occurs early in the inflammatory cascade. Therefore, downstream inhibition of inflammatory cell proliferation and cytokine release supports the use of abatacept early in the development of RA to maximize its benefits. This mechanism of action also explains the clinical data generated in the ATTEST study (Schiff et al. 2008 and 2009) where ACR responses tended to be faster with infliximab +MTX than abatacept + MTX in the first 3 months. However, by 6 months, the difference between the two active agents and placebo were similar. Importantly, clinical data show that efficacy with abatacept +MTX has been sustained in the majority of patients for up to 7 years, with high retention rates.	The Committee was aware that abatacept has a different mechanism of action to TNF inhibitors. The Committee agreed that there was no convincing evidence that abatacept plus methotrexate was more or less effective than other biological DMARDs plus methotrexate. See FAD section 4.6.
BMS & Otsuka Pharmaceuticals	The Committee discussed the issue of dose escalation of infliximab and have questioned whether the model used by BMS should also include dose escalation of abatacept. To clarify, dose escalation due to reduced response to infliximab over time (due to antibody formation against the murine component of infliximab, reducing the effective active agent in any given dose) is a recognised phenomenon (van Vollenhoven et al. 2004, Edrees et al. 2005, Ariza-Ariza et al. 2007, Blom M et al. 2010). Indeed, it is accepted as such by infliximab's manufacturers, their SPC stating *"If a patient has an inadequate response or loses response… consideration may be given to increase the dose step-wise…",* and has been documented by Singh et al. (2011) in the recent Cochrane review (see Figure above). Importantly, due to abatacept being a human fusion molecule, such a phenomenon is extremely unlikely to occur with this agent, and to date there are no abatacept data suggesting this position to be invalid. Thus, BMS consider their original stance to consider dose escalation for infliximab, but not for abatacept infliximab, to be valid.	The Committee discussed the decision problem and agreed that there was no clinically plausible reason related to route of administration that supports limiting the decision problem to people for whom subcutaneously-injected biological DMARDs is unsuitable. Because the Committee considered this decision problem not to be relevant for the NHS it concluded that it would not develop separate recommendations for people for whom self administration of subcutaneously-injected biological DMARDs is unsuitable. (See FAD section 4.13)
BMS & Otsuka Pharmaceuticals	The Committee agree that abatacept is clinically effective, as do the Clinical Experts. In their report the AG outline the clinical efficacy end points used in the clinical trials, and discuss the levels of improvement in the HAQ scores and DAS scores which are accepted as being clinically meaningful.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's

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	However, perversely, in their response the AG suggested that this substantial body of evidence, from clinical trials which were performed to internationally accepted standards, and which have been accepted by a number of different regulatory bodies, could be flawed. Their hypothesis is that the population in the studies did not reflect the actual rheumatoid population. The AG present no actual evidence as to what this "real world" population might be, or how they differ from the abatacept clinical trial population with regard to symptoms, disease status, posology and outcomes, or whether any subgroups from the abatacept trial population might reflect their preferred population. To disregard data from regulatory accepted clinical trials on the basis of an unsubstantiated hypothesised difference between populations would seem to be beyond the Committee's remit. Interestingly, the ACD report highlights the Expert Opinion that current clinical practice means that patients are receiving biological DMARDs much sooner than was previously the case. If one accepts the AG opinion alluded to in Paragraph 3.26 *(point above)* one might reasonably consider that the abatacept clinical trial population does actually reflect those patients in whom these treatments would be used in current clinical practice However, if one does not accept the AG argument (Paragraph 3.26), it should be noted that in the abatacept clinical trials the average duration of RA was 8 years prior to abatacept treatment. This duration, and associated disease progression, would imply that abatacept was assessed in a more refractory (challenging) population than is currently treated in clinical practice, yet was still shown to be clinically effective.	submission and the ERG report. The Committee noted the differing views of the ERG and the clinical specialists; the ERG's view was that the average participant in the trials had disease of shorter duration than the average UK patient and the clinical specialists' view was that the average participant in the trials had disease of longer duration than the average UK patient. The Committee therefore concluded that there was some uncertainty around the generalisability of estimates of effectiveness from the included trials to the UK population. See FAD section 4.3.
BMS & Otsuka Pharmaceuticals	The AG suggested that the accepted clinically relevant change in HAQ score (0.3) was not clinically meaningful**.** The threshold of 0.3 relies on previous published work, a point made by BMS in the responses to the ERG report. The AG present no evidence as to what they consider the level of change in HAQ scores should be in order to be clinically meaningful. At the TAC, the clinical experts suggested that 0.3 might actually be rather conservative (something with which BMS agree), with a level of 0.19-0.22 being cited as	Comment noted, this has been amended in the FAD, see section 3.31.

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	clinically meaningful (Goldsmith et al. 1993, Wells et al 1993, Kosinski et al. 2000, Cohen et al. 2003). Indeed, to compound their misunderstanding of the clinical assessment, the AG use 0.5 (considered "normalisation" by clinical experts) in their economic calculations. One can only assume that the AG thought this to be clinically meaningful; however it is not supported by evidence/data. Typically, registration biologic clinical trials have used 0.22 or 0.3, although 0.3 is considered the more robust by clinical experts.	
BMS & Otsuka Pharmaceuticals	The HAQ score has been used and accepted in numerous Appraisal Committees as the preferred assessment criteria to be used in the economic modelling. While DAS 28 had been used in abatacept clinical trials (as well as ACR), and clearly supports the clinical efficacy of abatacept, the AG suggest that BMS should have set a precedent by assessing abatacept's cost effectiveness using the DAS 28. If BMS had used DAS 28 instead of HAQ we presume the assessment group would also have found this equally wanting due to lack of precedent. Indeed, if the HAQ was inappropriate, it could be considered perverse that the Committee limit themselves to a single alternative scoring system to the HAQ. Abatacept has been shown to provide statistically significant improvements in RA patients with inadequate response to methotrexate in SF-36 across a range of health related quality of life (HRQoL) domains including: physical function; fatigue in all 8 domains of the SF-36; and the physical and mental component summaries (PCS and MCS) (Russell et al. 2006). Abatacept is also associated with substantive and significant improvements in the ability of patients to participate in their usual activities using the validated Activity Participation Questionnaire (APaQ) (Li et al in press). Similar significant improvements have also been found with abatacept treatment using other quality of life scales such as the sleep disturbance scale of Medical Outcomes Study Sleep (MOS-sleep) measure (Wells et al. 2010).	The Committee heard from clinical specialists that HAQ is not routinely used in clinical practice, DAS is more often used clinically to assess response to treatment, and HAQ is more often used in the research setting. The Committee considered that consistency had merits, but making a decision based on clinically meaningful outcomes was more important. The Committee expressed a preference for DAS28 as an outcome measure in economic models of rheumatoid arthritis, noting also that clinicians decide to stop or change treatment based on DAS (see FAD section 4.4).
BMS & Otsuka Pharmaceuticals	BMS agree with this assessment. Unfortunately, as highlighted by the Committee, such a population is likely to be very small – indeed the BMS data base on such contraindicated patients is very small – so the opinions of clinical experts will have to suffice in lieu of firm data.	Comment noted.
BMS & Otsuka	It is important to recognise abatacept has been shown to be an alternative to	The Committee agreed that there was no

Consultee	Comment	Response
Pharmaceuticals	infliximab, albeit with specific advantages with regards to clinical response over time and a favourable safety profile. Abatacept and infliximab were studied individually versus placebo + MTX in the same study. However as the study protocol was the same for both sets of groups they both reduced disease activity to the same extent at 6 months. However, after 1yr, patients on infliximab + MTX were switched to abatacept, with the majority of patients experiencing incremental improvements in the disease activity status. Indeed EPAR (Variation Assessment Report as adopted by the CHMP EMA/361627/2010) states abatacept has a similar short term efficacy profile but more favourable long-term efficacy. In addition, the recent Cochrane meta-analysis (Singh et al. 2011) found that abatacept was associated with fewer serious adverse events and fewer serious infections compared with the other biologics	convincing evidence that abatacept plus methotrexate was more or less effective than other biological DMARDs plus methotrexate. See FAD section 4.6. The Committee noted that these comments referred to a recently published network meta-analysis and Cochrane overview, which reported that abatacept was amongst the biological DMARDs for which no increased rate of side effects compared with placebo had been proven in the short term, whereas for others an increased rate was shown. However, the authors of the report expressed caution with interpreting these results because there was no consistency across the outcomes, and concluded that people who take biological DMARDs will probably experience more side effects or drop out of the study due to side effects than people who take placebo. The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus methotrexate. (see FAD section 4.10)
BMS & Otsuka Pharmaceuticals	The Committee also discussed the vexed topic of infliximab vial sharing. BMS' position is that there are no hard data on this issue. The discussions at the TAC showed that clinical opinion is not based on firm evidence. There are no data to show that such a practice is widespread, and one which is	The Committee discussed the decision problem and agreed that there was no clinically plausible reason related to route of administration that supports limiting the decision problem to people for whom

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	formally supported by hospital, clinical and pharmacy practice. Indeed, it was also suggested by one of the clinical experts that "rounding up" of infliximab vial content might just as easily occur. It would seem perverse to base clinical practice (as reflected in the model) on hypothetical discussions at best , and "bad practice" at worst.	subcutaneously-injected biological DMARDs is unsuitable. Because the Committee considered this decision problem not to be relevant for the NHS it concluded that it would not develop separate recommendations for people for whom self administration of subcutaneously-injected biological DMARDs is unsuitable.
BMS & Otsuka Pharmaceuticals	Importantly, the Clinical Experts consider choice to be paramount. Indeed, BMS consider it to be essential offer the choice of an alternative biologic to those patients in whom infliximab has been shown to be ineffective, or in whom conventional TNF inhibitor agents are contraindicated, **as these patients really do not have any other treatment option.** Rituximab, the only other biological of possible choice, has no data to support its use in this situation, and is anyway not licensed as a first line biologic therapy.	When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of evidence it is not possible to refer to a precise figure. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available, whose health status is not comparable to the overall trial population, who have very complex medical needs, and where any decision on the use of biological treatments would require a careful balance of the potential benefits and harms for the individual patient. (See FAD section 4.18 and 4.20)
	Finally, in a recent Cochrane review (Singh et al 2011) abatacept was shown to be associated with a significantly lower risk of serious adverse events compared with most other biologics used in RA. Indeed, abatacept was considered significantly less likely than infliximab to (a) be associated with serious adverse events, (b) serious infections and (c) result in withdrawals due to adverse events. Because of these recent Cochrane findings it would seem perverse, given that the ATTEST study (Schiff et al 2008 and 2009) showed abatacept and infliximab reduced disease activity to the same extent, that abatacept should not be available to RA patients in whom infliximab has proved inadequate – whether due to reduced clinical	The Committee noted that these comments referred to a recently published network meta-analysis and Cochrane overview, which reported that abatacept was amongst the biological DMARDs for which no increased rate of side effects compared with placebo had been proven in the short term, whereas for others an increased rate was shown. However, the authors of the report expressed caution

Consultee	Comment	Response
	effectiveness resulting in dose escalation, or due to the increased likelihood of side effects. In summary, as confirmed by Expert Opinion, abatacept should be available to be used by patients who cannot be treated by a TNF inhibitor. It is an effective and better tolerated alternative to infliximab, and would give patients and physicians a valuable therapeutic biologic option.	with interpreting these results because there was no consistency across the outcomes, and concluded that people who take biological DMARDs will probably experience more side effects or drop out of the study due to side effects than people who take placebo. The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus methotrexate. (see FAD section 4.10)
BMS & Otsuka Pharmaceuticals	Using a non-linear approach to map HAQ scores to EQ-5D utility values is one that has been accepted by previous Appraisal Committees and has become an accepted methodology. For example, in the appraisal leading to the publication of TA 130 it was noted (section 4.3.10 pg 27); *"The Committee was aware of the limitations of using HAQ scores as a basis for estimating health-related quality of life in patients with RA. Namely that the HAQ is a measure of functional disability, which fails to capture the psychological and pain elements of quality of life associated with RA. In addition, the Committee noted that the HAQ scoring system may be an insensitive measure of small changes in health-related quality*	The Committee was aware of the manufacturer's sensitivity analysis that showed mapping using a linear utility increased the ICER for abatacept plus methotrexate compared with conventional DMARDs plus methotrexate from £29,700 per QALY gained in the base case to £32,100 per QALY gained. The Committee concluded that although it was not unreasonable to use a non-linear function, the use of a linear function could also be considered plausible, and therefore this increased the uncertainty around the ICERs. (see FAD section

Consultee	Comment	Response
	of life and may have a non-linear relationship to utility scores. The Committee noted that HAQ had been used as a basis for calculating utility across all the economic models, and while noting its limitations, accepted that it was the best means of estimating utility for the purposes of the economic analysis given the available data". This approach of mapping HAQ to EQ-5D has also been described in the literature (Barton et al 2004); *"However, it is possible that a better fit can be obtained from a non-linear relationship".* BMS consider it perverse and unfair to compare abatacept against recommended products which have been approved utilising agreed methodologies, and then to refuse abatacept based on those same methodologies. BMS also consider it unjustified, in light of the above evidence, that an alternative methodology is suggested based solely on its effect on the resultant ICER, rather than using a scientific methodology based on its own merit in order to produce a valid ICER.	4.8).
BMS & Otsuka Pharmaceuticals	BMS acknowledge that including productivity costs in the economic model was outside the reference case as defined by NICE. These costs were included in error. BMS therefore accept the additional analyses presented by the ERG utilising £1120 per HAQ unit. It is pertinent to note that with this amendment that abatacept remains cost effective against DMARDs.	The Committee considered the costs included in the economic model. The Committee heard the manufacturer acknowledge that it had used costs that included loss of productivity, and that this was outside the reference case defined by NICE. (see FAD section 4.11)
BMS & Otsuka Pharmaceuticals	It is very unlikely that abatacept, which is a human fusion molecule, could cause neutralising antibody production, which is the biological phenomenon which causes reduced efficacy in a biologic (which necessitates dose escalation). Indeed, data from the abatacept clinical studies show that such a phenomenon does not occur. In abatacept treated patients the immunogenicity rate is very low, and there has been no report showing that it translated into a loss of efficacy (Haggerty et al. 2006, Haggerty et al. 2007). Clinical trials experience has shown a sustained efficacy over 7 years (see Figure below) (Westhovens et al. 2009a) and a high retention rate of abatacept in the long-term extension of a number of trials (Westhovens et al.	Comment noted.

Consultee	Comment	Response
	2009, Kremer et al. 2009). BMS therefore consider it would be inappropriate to include dose escalation of abatacept within the economic model.	
BMS & Otsuka Pharmaceuticals	The mixed treatment comparison was produced in a robust and scientific manner. In addition the network of studies included in the MTC was validated using an advisory panel of 4 expert clinicians and a statistician in order to ensure that no studies were omitted.	The Committee agreed that there was no convincing evidence that abatacept plus methotrexate was more or less effective than other biological DMARDs plus methotrexate. See FAD section 4.6.
BMS & Otsuka Pharmaceuticals	Using the HAQ score for the purposes of economic modelling of RA has been used and accepted during numerous technology assessments for treatments for RA. Whilst the DAS 28 is more often used in clinical practice than the HAQ, and may give a better day to day clinical picture of the disease, the HAQ allows a better mapping to utilities. This has been well established, and used extensively for a number of years (Barton et al 2004). Importantly, there are two ways of calculating DAS score, (1) by using the ESR and (2) using CRP. In contrast, there is only one method by which to measure HAQ. This means that the DAS 28 scores very much depend on the chosen method of measurement, which is not always reported, and so will affect associated utilities in an inconsistent way. Indeed, the Technology Assessment Group (TAG) used this methodology in both TA130 (2007) and TA195 (2010). Using a non-linear approach to map HAQ scores to EQ-5D utility values is one that has been accepted by previous Appraisal Committees and has become an accepted methodology. In TA130 the committee noted, that while this methodology had its limitations, they accepted that it was the best means of estimating utility for the purposes of the economic analysis of RA given the available data. The mortality rate for each unit increase in HAQ score was taken from the published literature which is the currently the only source available for this information. However different mortality rates were presented as sensitivity analysis.	Comments noted; see individual responses above.

Consultee	Comment	Response
	The exclusion within the economic model of costs and the associated disutility related to adverse events is a conservative approach. A recent independent meta-analysis (Singh et al 2011) supported abatacept's favourable safety and tolerability profile, specifically in regard to serious infections. This is also supported by EPAR 2010 (Variation Assessment Report EMA/361627/2010). Therefore it is likely that the inclusion of adverse events in the model would see a reduction in the ICER in favour of abatacept. BMS acknowledge that including productivity costs in the economic model was outside the reference case as defined by NICE. These costs were included in error. BMS therefore accept the additional analyses presented by the ERG utilising £1120 per HAQ unit. It is pertinent to note that with this amendment at abatacept remains cost effective against DMARDs.	
National Rheumatoid Arthritis Society	We do not think that all the relevant evidence has been taken into account and agree with the British Society for Rheumatology's response to the ACD that some of trial evidence has been either misinterpreted or simply not adequately factored into the health economic calculations in respect of cost effectiveness. Also, we do not believe that the Committee have adequately taken into account the quality of life issues for someone with RA who may be contra-indicated for Anti TNF post DMARD failure. I know first-hand how vital biologic therapies are for those who have failed on standard DMARDs. The majority of people are able to start Anti-TNF treatment in line with NICE guidance, however, for a small minority, for whom Anti-TNF is contra-indicated, Abatacept is a potential lifeline and I hope that NICE will look again at the data and some of their assumptions. I believe the Committee is well aware that for this group of patients, asking them to continue on DMARDs when they have failed at least two including methotrexate and have a DAS score of greater than 5.1 is condemning them to a life of pain and misery, with worsening disease which delivers no quality of life. I had to come off my treatment for 12 weeks last year and found that my pain levels increased so significantly that even morphine was inadequate. I could not imagine remaining in that state for any length of time, let alone for the rest of my life. Steroids are not recommended to be taken long term and this is reinforced in the NICE RA guidelines , quite rightly so,	When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of evidence it is not possible to refer to a precise figure. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available, whose health status is not comparable to the overall trial population, who have very complex medical needs, and where any decision on the use of biological treatments would require a careful balance of the potential benefits and harms for the individual patient. (see FAD section 4.18 and 4.20).

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	as we are now very aware of their unacceptable side effects over time. Yet high dose steroids is likely to be the only course of action to relieve the pain for someone meeting the threshold for Anti-TNF, but unable to have one of these drugs.	
National Rheumatoid Arthritis Society	In point 4.12 the BSR have addressed in their response the argument which has been prosecuted many times about the difference in responsiveness to HAQ of patients with short duration disease whose disease is being driven by inflammation against those with much longer duration whose HAQ is being driven by mechanical damage and therefore less likely to respond to treatment. We support their assertion that HAQ changes derived from these trials will be an underestimate of the changes seen in patients with earlier disease in routine care today, and thus the ICER for routine care today is likely to be lower than the base case ICER of £29,700. The committee questioned the patient experts during the Appraisal about the scenario where having a quality of life could be worse than being dead and this is certainly the case. I know of people who have attempted suicide and have certainly had letters and emails from people who are experiencing a 'living hell' when no suitable and effective treatment can be found which is extremely hard to bear, especially when you know there are treatments which, if available, might be effective. There are two additional benefits to Abatacept which we would like to reinforce, firstly that it can be taken as monotherapy if methotrexate is also counter-indicated or not tolerated, and the evidence that it delivers increased benefit after 12 months which should be taken into account.	The Committee heard that managing rheumatoid arthritis has changed in line with NICE guidance, and that clinicians start treatment with conventional DMARDs or TNF inhibitors sooner after diagnosis than in the past. Therefore, the characteristics of people treated with biological DMARDs in the UK have changed (see FAD section 4.3). The Committee therefore concluded that there was some uncertainty around the generalisability of estimates of effectiveness from the included trials to the UK population. (see FAD section 4.3). The Committee heard from the patient experts and noted from the consultation comments that it was possible that some people with rheumatoid arthritis may experience such a low quality of life. (see FAD section 4.8). Comment noted. Abatacept is currently licensed only in combination with methotrexate. The Committee is unable to make recommendations about the use of technologies outside of their current marketing authorisation. (See section 6.1.8 of the NICE methods guide).
National Rheumatoid Arthritis Society	Whilst NICE may not be discriminating against the group of patients for whom Anti-TNF is contra-indicated on any of the above grounds, we believe that they would suffer discrimination on grounds of health which we feel is equally unfair. Clinical guidelines from BSR, EULAR and ACR allow the use of Abatacept as a first line biologic post DMARD failure	When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of

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	and we are talking about a relatively small group of people so costs would be contained. We agree with the BSR that there is a significant body of evidence to support the use of Abatacept in this important group of patients and we hope that the Committee will re-consider their guidance and allow at least this restricted use of Abatacept.	evidence it is not possible to refer to a precise figure. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available, whose health status is not comparable to the overall trial population, who have very complex medical needs, and where any decision on the use of biological treatments would require a careful balance of the potential benefits and harms for the individual patient. (see FAD section 4.18 and 4.20)
British Society for Rheumatology	This commentary is focussed on the use of Abatacept in patients with rheumatoid arthritis (RA) who: • have a DAS>5.1 despite treatment with two conventional DMARDS (including Methotrexate) • have a contraindication to the use of TNF antagonists. This group of patients will not progress well if they continue with DMARDs alone, and are likely to accumulate irreversible joint damage due to inadequate suppression of inflammatory disease activity. This not only impacts on their joints, but there is increasing evidence for the effects of inadequate disease control on mortality, with increased cardiovascular disease in patients with ongoing raised inflammatory markers. Current NICE TAs do not allow the use of any of the alternative biologic therapies unless TNF antagonists have been used. Thus patients with a contraindication to TNF antagonists may not be given the chance of responding to Abatacept despite this agent being licensed in the DMARD inadequate responder population. Sections 4.9 – 4.19 discuss the use of Abatacept in this scenario. The base case ICER of £29,700 after the ERG had corrected for arithmetical errors in the manufacturers submission is noted. This figure could represent	The Committee heard from the clinical specialists that some people have contraindications to treatment with a TNF inhibitor including heart failure, sepsis, or malignancy. The Committee noted that congestive heart failure was not listed as a contraindication in the SPC for etanercept. Therefore, the Committee considered that for people with moderate to severe congestive heart failure, for abatacept the appropriate comparator (treatment option) would be etanercept. (see FAD section 4.14/15) When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of evidence it is not possible to refer to a precise figure. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available, whose health status is not comparable to the overall trial population, who have very complex medical needs, and where any decision on the use of biological treatments would

Consultee	Comment	Response
	an effective use of NHS resources, being in the region of ICERs that have previously been accepted as representing value to the NHS. 4.12 – The HAQ scores used in the model are derived from patients in clinical trials with a much longer disease duration (Phase IIb 9 yrs, AIM 8 YRS, ATTEST 8 yrs) at study entry than that in clinical practice today where the time to first biologic in patients poorly responsive to conventional DMARDs (i.e. persistent DAS>5.1) can be as little as 1 year. A disease duration of ~ 8 years will be associated with the accrual of irreversible damage which will constrict the responsiveness of the HAQ score to therapies. Therefore HAQ changes derived from these trials will be an underestimate of the changes seen in patients with earlier disease in routine care today, and thus the ICER for routine care today is likely to be lower. 4.13 – The implication of the text is that the committee viewed with scepticism the extremely poor quality of life associated with rheumatoid arthritis when HAQ is mapped to EQ-5D. As such it seems that the committee favour an alternative (non linear) approach to mapping which diminishes this effect and increases the ICER. There is no rationale given to accept or reject this alternative, beyond the (lack of) willingness to accept that a person with RA may have a quality of life worse than being dead. This is a speculative interpretation of the data, of insufficient merit to change the ICER from the base case of £29,700. 4.15 – Abatacept is unique amongst biologics in consistently showing incremental benefit beyond 1 year in most of the clinical trials. The disease may therefore be expected to get better with time, yet the model takes no account of this. This omission will not favour the benefits of Abatacept, and as such the ICER is likely to be lower. 4.16 – Adverse events are lower for Abatacept than other biologics, and	require a careful balance of the potential benefits and harms for the individual patient. (see FAD section 4.18 and 4.20). Comment noted. The Committee heard from the clinical specialists that starting treatment with a biological DMARD sooner may increase a person's potential to benefit from treatment, because he or she is likely to have less irreversible joint damage. The Committee concluded that the difference in the duration and severity of rheumatoid arthritis could limit the generalisability of the estimates of effectiveness from the included trials to the UK population.. (see FAD section 4.3). The Committee was aware of the manufacturer's sensitivity analysis that showed that using a linear utility mapping increased the ICER for abatacept plus methotrexate compared with conventional DMARDs plus methotrexate from £29,700 per QALY gained in the base case to £32,100 per QALY gained. The Committee concluded that although it was not unreasonable to use a non-linear function, it introduced uncertainties into the ICERs. (see FAD section 4.15). The Committee also noted the response to consultation that abatacept is unique amongst other biologic DMARDs in showing incremental benefit beyond one year, however it was aware that it had not been presented with any comparative data to support this point. (see FAD section 4.16). The Committee noted that these comments referred to a recently published network meta-analysis and Cochrane overview, which reported that abatacept was amongst the biological DMARDs for which no

Consultee	Comment	Response
	remain similar to DMARDs in long term extension studies (up to 7 years). An assumption that they are likely to rise in line with other biologics is not founded on evidence, and provides no justification to assume a rise in the base case ICER above £29,700 4.17 –Comments regarding the plausibility of having to increase the dose of Abatacept with time based on the necessity to do this with other biologic agents (e.g. Infliximab) are unsupported by clinical evidence. They also contradict the clinical trial observations of an incremental benefit beyond 1 year of Abatacept treatment, which in turn might permit a dose reduction with time. Thus, speculation of dose changes over time are more likely to result in an improvement in the ICER following a dose reduction, than a worsening of the ICER following a dose increase. In light of these points the committee's assertion that the alternative scenarios proposed are 'more realistic' or contain 'plausible assumptions', which will always lead to an increase in the base case ICER, are not a	increased rate of side effects compared with placebo had been proven in the short term, whereas for others an increased rate was shown. However, the authors of the report expressed caution with interpreting these results because there was no consistency across the outcomes, and concluded that people who take biological DMARDs will probably experience more side effects or drop out of the study due to side effects than people who take placebo. The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus methotrexate. (see FAD section 4.10) The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment Report. Recommendations are based on evidence of both clinical and cost effectiveness.

Consultee	Comment	Response
	reasonable interpretation of the evidence. Instead no alteration or an improvement in the ICER is more likely in several of these scenarios. In conclusion, the base case ICER does support the use of Abatacept for the relatively small number of patients who are eligible for anti-TNF therapies but are contraindicated. These patients will not do well with continued conventional DMARDs, yet marketing authorisation and guidelines from BSR, EULAR and ACR permit the use of Abatacept as a first line biologic at this stage. The ACD relies upon many assumptions to reach its conclusions, some of which misrepresent the clinical trial evidence, as outlined. There is a significant body of evidence to support the use of Abatacept in this important group of patients, with respect to efficacy, safety, retention and incremental benefit, and insufficient evidence to justify the assumptions that the base case ICER is likely to be higher than the quoted figure of £29,700.	
Arthritis Care	Arthritis Care is very disappointed that NICE proposes not to support the use of abatacept, in circumstances where conventional DMARDS have failed. We are very concerned that this draft decision by NICE may result in many people suffering avoidable pain. We are concerned that cost considerations play too high a role in this decision, and the potential benefit to patient - of clinicians having another pharmaceutical option available as a treatment option - have been given too low a one. We have continuously emphasised the need for a wide choice of treatment for people with RA. While there are a number of drugs currently available for people with RA, we know that anti - TNF drugs vary substantially in their efficacy: different drugs work differently for different people, and having access to the widest range of treatment options gives someone with RA the best chance of good control of this disabling disease. This draft guidance limits that choice, and so risks condemning a large number of people with RA to living in pain. Clinicians stress the importance of being able to try different anti-TNF	The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations. The Committee heard from clinical specialists and patient experts of the importance of having a choice of treatment for people whose disease has not responded adequately to initial treatment with conventional DMARDs. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 5). Comment noted. The Committee was aware of the response from consultation that patients may have a strong preference for a different form of administration. The Committee was aware that the manufacturer proposed that the population for whom subcutaneous therapy is unsuitable would include people with needle phobia or needle

Consultee	Comment	Response
	treatments for individual patients. In response to a proposed appraisal in 2008 to restrict the options for anti-TNF treatment Professor Rob Moots, a clinician and Professor of Rheumatology at the University of Liverpool, commmented “it’s almost impossible to know which anti-TNF will work for a patient at the outset” He went on to describe the NICE appriasal as “flying in the face of clinical judgement”, and stated that “many patients will be left in astonishing pain”. This decison appears to produce the same end result: with repect to a proportion of their RA patients, clinicians will be left knowing that they have been unable to explore all the options potentially available to them for effective treatment. There is also hard evidence to support the position that abatacept is effective in some cases. A study conducted in 2006 found that “combined abatacept and methotrexate treatment provided significant improvements to patients with RA, including both physical and mental health, physical functioning, and fatigue.” In support of its decision, NICE states that “few people experience problems handling the injection devices required for other, currently available treatments”. Yet NICE also reports that “the Committee heard from patient experts that people do care whether therapies are injected intravenously or subcutaneously”. This response appears in the first instance to be irrational, given, as NICE notes, that the intravenous method also involves use of needles. However, it remains the case many people report finding the subcutaneous method difficult, and may have a strong preference for a different form of administration, such as an infusion, which is more convenient for their needs. We urge NICE to revisit this evidence, and reconsider a decision which risks denying many people with RA the potential life-changing benefits of this drug.	aversion. However, the Committee concluded that people with needle phobia could have a similar problem with intravenous therapy, and if necessary could possibly be assisted by a nurse or family member. The Committee was aware that psychological treatments for needle phobias and aversion exist. (see FAD section 4.13).
Royal College of Nursing	The ERG notes that people included in the trials had not had rheumatoid arthritis (RA) for as long or had as many conventional DMARDs as those in clinical practice. We would argue that the shorter time on a conventional	The Committee heard that the management of rheumatoid arthritis has been changing in line with NICE guidance, and that clinicians start treatment

Consultee	Comment	Response
	DMARD and the use of fewer DMARDs reflects current clinical practice and reflects NICE guidance (CG79) on the treatment of RA (NICE 2009). Clinicians are starting biologic therapies sooner in the disease history than in the past. The ERG assumes the sharing of vials in larger organisations. The sharing of vials is poor clinical practice and is strongly advised against by our pharmaceutical colleagues due to the risk of cross infection.	with conventional DMARDs or TNF inhibitors sooner after a person's diagnosis of rheumatoid arthritis than in the past. (see FAD section 4.3) The Committee concluded that the question of the cost effectiveness of abatacept plus methotrexate compared with infliximab plus methotrexate for people for whom self-administration of subcutaneously-injected biological agents is unsuitable is not relevant for the NHS. (see FAD section 4.13).
Royal College of Nursing	The ERG states that an improvement of HAQ of 0.3 is not clinically significant. The RCN Rheumatology Forum (RCN RF) would argue that this can mean a huge improvement in function for some patients and therefore is clinically significant. The value of the ICERS is similar to biologic therapies already in use and approval of those drugs was based on the optimistic scenario. We feel that the same should be applied in the use of Abatacept. This would give a QALY of £27, 157 (ScHARR) pg 133-134 based on no vial sharing.	FAD section 3.31 states that "The ERG highlighted that although this was based on the endpoints of the key trials, the confidence intervals are such that an improvement of 0.3 in HAQ score may not be statistically significant." Comment noted.
Royal College of Nursing	No. The proposals appear to disregard the fact that Abatacept targets a different cytokine (T cells) to the other biologic therapies. By not recommending this treatment for use, NICE is depriving those patients who clinicians feel would not respond to current biologic therapy the chance of using Abatacept as a first choice. RA is a heterogeneous condition and the need for access to drugs that work on different aspects of the inflammatory pathway is vital in treating and controlling this condition. Abatacept appears to work equally well in people who are sero positive or sero negative. Clinicians need to gain experience of using other drugs than TNF inhibitors as first line treatment after the failure of conventional DMARDs. THE RCN RF feels strongly that there is sufficient evidence to approve this	Comment noted. The Committee was aware that abatacept has a different mechanism of action to TNF inhibitors, because it affects the co-stimulation of T-cells. The Committee considered the contraindications listed in each drug's SPC, and discussed whether people for whom treatment with a TNF inhibitor is contraindicated represented a clearly defined and identifiable population relevant for clinical practice in the NHS. (see FAD section 4.14 and 4.16)

Consultee	Comment	Response
	drug for use after conventional DMARDS.	
Royal College of Nursing	We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that an analysis of equality impact have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. Any guidance on the use of this technology should also be mindful of the impact it may have on reducing socio-economic inequalities.	The Committee considered whether NICE's duties under the equalities legislation required the Committee to alter or to add to its recommendations. (see FAD sections 4.19 and 4.20)

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None		

Comments received from commentators

Commentator	Comment	Response
Pfizer	Pfizer welcomes the opportunity to comment on the ACD and the evaluation report of abatacept for the treatment of Rheumatoid Arthritis (RA) after the failure of conventional disease-modifying anti-rheumatic drugs (DMARDs). Overall we agree that the provisional recommendations for abatacept for this indication are sound and are a suitable basis for guidance to the NHS. We note from the ACD that there are 3 potential decision populations that have been included in this appraisal: 1. The population originally specified in the NICE scope for this appraisal, which specified abatacept should be compared with other biological DMARDs or conventional DMARDs in people with moderate and severe active RA who had responded inadequately to previous therapy with one or more conventional including methotrexate (MTX). 2. The manufacturer, then, specifically focused their submission of abatacept in comparison with infliximab in a subpopulation of people who may not be able to use subcutaneous therapies. 3. An additional decision problem was posed by clinical experts which compares abatacept with conventional DMARDs, but only in a subpopulation of people for whom clinicians consider TNF inhibitor treatment inappropriate because of a contraindication. Accordingly, we believe that etanercept should only be considered as a comparator to abatacept if the original scoping population remains applicable. If this is the case, then, our specific concern about the appraisal is the inclusion of the TEMPO trial in the manufacturer's mixed treatment comparison (MTC) and the use of the current MTC results in the economic model. In addition, we have identified a number of issues/errors in our review of the evaluation report and these are summarised in appendix 1 of our response.	The Committee heard from the clinical specialists that some people have contraindications to treatment with a TNF inhibitor including heart failure, sepsis, or malignancy. The Committee noted that congestive heart failure was not listed as a contraindication in the SPC for etanercept. Therefore, the Committee considered that for people with moderate to severe congestive heart failure, for abatacept the appropriate comparator (treatment option) would be etanercept. (see FAD section 4.14) The Committee noted that the manufacturer omitted key trials from the network and incorporated trials with different patient populations. The Committee also considered a consultation comment expressing the concern that one of the trials included participants whose disease had inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution. (See FAD section 4.6).

Commentator	Comment	Response
Pfizer	Pfizer notes that the manufacturer acknowledges in 5.7.1 of their submission document that TEMPO 'may have included a different study population to the other studies, as the patient population included was not composed of inadequate responders to methotrexate, but to conventional DMARDs.' We would argue that TEMPO is fundamentally different from all the comparator biologic DMARD trials in this analysis since patients did not need to have demonstrated an inadequate response to MTX at baseline. These participants were more likely to benefit from MTX and as a result the observed placebo response reported in this trial was higher than in other biological DMARD trials. Pfizer would recommend that that TEMPO should be excluded from the abatacept MTC, as it also does not meet the population of interest specified in the NICE scope, which is 'adults with RA who have had an inadequate response to one of more conventional DMARDs including MTX.' Furthermore, NICE in previous published appraisals for RA treatment tocilizumab (TA198) and certolizumab pegol (TA186) and the NICE ACD for golimumab after failure of previous anti-rheumatic drugs has noted that the TEMPO trial was different from other biologic DMARD trials because of the unusually high placebo response rate. NICE has previously requested that it should be excluded from the analysis. Therefore, to be consistent with previous NICE appraisals this trial needs to be removed from the analysis or a scenario analysis conducted with it removed.	The Committee noted that the manufacturer omitted key trials from the network and incorporated trials with different patient populations. The Committee also considered a consultation comment expressing the concern that one of the trials included participants whose disease had inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution. (See FAD section 4.6).

Commentator	Comment	Response
Pfizer	We would like to highlight that the efficacy estimates of certolizumab pegol with MTX in the MTC may lead to an overestimation of its benefit and these should be treated with caution due to the uncertainty around its true benefit. • Patients were excluded 8 weeks before the primary efficacy endpoint and treated as non responders. However in these 8 weeks it is possible that some patients would have achieved an ACR20 response and were incorrectly assumed to have a no response. This is likely to affect the control arm to a greater extent due to the higher withdrawal rate (63-81%) compared to the intervention arms (17-21%). It has been shown that methotrexate is most effective when step-up therapy is employed (as it is in the majority of other trials). The restriction on dose increases may have resulted in patients being taken into rescue therapy from the control arm that would have responded by week 24. This would result in a greater difference between certolizumab pegol efficacy and that seen in the control arm.	The Committee noted that the manufacturer omitted key trials from the network and incorporated trials with different patient populations. The Committee also considered a consultation comment expressing the concern that one of the trials included participants whose disease had inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution. (See FAD section 4.6).
Pfizer	The primary end point for ATTRACT trial is at 30 weeks for ACR20, but the inclusion criteria that the manufacturer has used for ACR response is 24/28 weeks. This trial therefore falls outside the inclusion criteria of the analysis and thus we question its inclusion.	The Committee noted that the manufacturer omitted key trials from the network and incorporated trials with different patient populations. The Committee also considered a consultation comment expressing the concern that one of the trials included participants whose disease had inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution. (See FAD section 4.6).
Pfizer	There is evidence from European registries and observational data that suggests that the time on treatment for biologic DMARDs (predominantly adalimumab, etanercept and infliximab) is not the same, for example, in the Danish DANBIO, Swedish SSATG and Italian Lorhen registries. We note that the manufacturer assumed the same time on treatment for all biologics. We argue that this fails to address the evidence and accordingly the uncertainty that time on treatment for biologic DMARDs may not be the same.	The Appraisal is based on the available evidence submitted to the Institute by the manufacturer, statements by the experts and the review of the Evidence Review Group. The evidence referred was not included.

Commentator	Comment	Response
Pfizer	We understand the manufacturer's rationale for using HAQ as the initial response to biologic therapy in the economic model given the limited availability of DAS 28 outcomes reported in randomised clinical trials (RCTs). However, we would argue that ACR response should also be considered in the economic model because: • There are a similar number of RCTs that report ACR, when compared to the number reporting HAQ, in the manufacturer literature search for the MTC. The evidence base is therefore similarly strong for both disease specific measures. ACR is, also the primary endpoint in the majority of trials. • The use of ACR, as an initial response has been used in a number of previous recent NICE appraisals in RA, notably certolizumab pegol, tocilizumab and golimumab. We suggest that to allow comparison between different NICE appraisals there needs to be consistency in the evidence appraised. We acknowledge that using ACR instead of HAQ leads to additional uncertainty through mapping between the disease specific measures. But, a more appropriate approach, we would argue is to try both HAQ and ACR response separately as the initial response to treatment, in order, to fully explore the sensitivity of initial efficacy estimates on the abatacept economic model's results.	The Committee heard from clinical specialists that HAQ is not routinely used in clinical practice, DAS is more often used clinically to assess response to treatment, and HAQ is more often used in the research setting. The Committee expressed a preference for DAS28 as an outcome measure in economic models of rheumatoid arthritis, noting also that clinicians decide to stop or change treatment based on DAS. (see FAD section 4.4)
Abbott	Abbott is unaware of any relevant evidence that the Committee has not taken into account	Comment noted.

Commentator	Comment	Response
Abbott	Section 4.9 of the ACD states that "The Committee was aware that in practice these people may receive rituximab". Although this paragraph also goes on to state that "the Committee acknowledged that in strict accordance with the marketing authorisation and the NICE recommendations for rituximab, people must have disease that has shown an inadequate response, or be intolerant to, TNF inhibitors to receive rituximab", Abbott is concerned that this statement may be seen to encourage off-licence use of rituximab in a population in which the European Medicines Agency (EMEA) has expressed concerns around the risk benefit profile. In 2010 the EMEA considered the use of rituximab in patients who have not previously received an anti-TNF. Following a full review of the evidence, the CHMP concluded that "the benefit-risk balance for rituximab in MTX-naïve patients (1st line treatment) and in MTX-IR patients (2nd line treatment) was not favourable and that the therapeutic efficacy has not been properly and sufficiently demonstrated."(p53 EPAR) The EPAR reports that "a major concern was raised as long-term safety data in the sought indications were lacking, and the consequences of long-term consequences of long-term B-cell suppression in the RA population were unclear". They also noted that "the efficacy data to support the 1st and 2nd line treatment was insufficient", and "the effect of rituximab on prevention of radiographic progression seems less than reported for TNF-alpha blockers". The manufacturer subsequently withdrew their application for a licence extension, and have informed NICE that they "will not be seeking a license for this particular indication at the present time".	The Committee was aware that NICE recommends adalimumab plus methotrexate, etanercept plus methotrexate, infliximab plus methotrexate (TA130) or certolizumab pegol plus methotrexate (TA186) as treatment options in the clinical pathway at the same point at which abatacept is considered in this appraisal. (see FAD section 4.12). The Committee considered that for people with moderate to severe congestive heart failure, for abatacept the appropriate comparator (treatment option) would be etanercept. (see FAD section 4.14) The Committee was aware that although etanercept is not contraindicated in congestive heart failure, the etanercept SPC includes a special warning and precaution for use of etanercept in people who have congestive heart failure. The Committee considered that if etanercept were considered unsuitable, then for abatacept the appropriate comparator (treatment option) for this decision problem would be conventional DMARDs. (see FAD section 4.16)
Abbott	Abbott can understand why the Committee has made its preliminary recommendations for abatacept.	Comment noted.
Abbott	Abbott is not aware of any equity related issues that may need special consideration in the preliminary recommendations.	Comment noted.

Commentator	Comment	Response
CSAS	On behalf of the Commissioning Support, Appraisals Service (CSAS), I would like to submit our comments on the appraisal consultation document for the Single Technology Appraisal on Abatacept for treatment of rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs in the NHS in England and Wales. CSAS is in agreement with the appraisal committee's decision that this technology does not represent a cost effective use of scarce NHS resources.	Comment noted.
CSAS	Unit costs: Abatacept is supplied in 250mg vials at a cost of £242.17 (excluding VAT; 'British National Formulary' BNF edition 61) and the prescribed dose is 500-1000mg (10mg/kg) administered on weeks 0, 2, 4, and thereafter every 4 weeks.	Comment noted.
CSAS	Affordability: The CSAS rapid evidence review estimated that an average PCT of 300,000 could expect to have 2400 people with rheumatoid arthritis, 10% of whom would be eligible for biologicals, and 49% of whom approximately 118 patients - would be able to take and tolerate methotrexate alongside abatacept. The manufacturer has estimated that the annual drug cost for a person weighing between 60 and 100kg will be £10,171 in the first year and £9,445 in subsequent years. The estimated annual cost to treat 118 patients based on this revised costing is £1.2 million in the first year and £1.1 million annually thereafter. The Evidence Review Group (ERG) also estimates the cost per administration at £158.	Comment noted.

Commentator	Comment	Response
CSAS	Efficacy: The ERG discussed the four RCTs identified in the manufacturer's submission and the mixed treatment comparison. In three RCTs (AIM, Kremer and IM101-119), abatacept plus methotrexate proved superior to placebo plus methotrexate in reducing disease activity; only AIM and Kremer were included in quantitative analyses. One three-arm RCT compared abatacept with placebo and with infliximab (all plus methotrexate; the ATTEST trial), and found abatacept to have better efficacy than infliximab. Both the AIM and the ATTEST studies found that abatacept plus methotrexate reduced disease activity at six months compared with placebo plus methotrexate (mean difference in DAS28 [28-joint disease activity score] vs. placebo: AIM, n=656: -1.15, 95% CI -1.38 to -0.91; ATTEST, n=431: -1.04, 95% CI -1.42 to -0.67). More patients treated with abatacept showed an improvement in disease activity, measured as DAS28 change ≥1.2 (RR vs. placebo: AIM: 1.62, 95% CI 1.39 to 1.88; ATTEST: 1.58, 95% CI 1.29 to 1.93). Several other DAS parameters and measures of disease activity using American College of Rheumatology (ACR) response criteria ACR20/50 and 70 were improved with abatacept at six months and at one year follow-up. There was greater improvement in HAQ (Stanford Health Assessment Questionnaire) disability score at six months and one year with abatacept versus placebo and meta-analysis undertaken by the ERG estimated relative improvements in clinically meaningful HAQ response with abatacept versus placebo (six months: RR 1.46, 95% CI 1.27 to 1.67; one year: RR 1.65, 95% CI 1.41 to 1.94). The manufacturer's mixed treatment comparison of 11 trials comparing abatacept plus methotrexate with five biological DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) plus methotrexate, demonstrated similar efficacy of abatacept to most other DMARDs, and better efficacy of abatacept compared with that in the trials included in meta-analysis. As the mixed treatment comparison also omitted key trials and included trials of participants with different baseline characteristics it was viewed with caution by the Appraisal Committee	Comment noted.

Commentator	Comment	Response
CSAS	Quality of the evidence: The quality of the three trials included in quantitative analysis was fully assessed by the manufacturer and by the evidence review group. The included studies have also been appraised by Cochrane reviewers in a recent review of abatacept for rheumatoid arthritis. Both the Kremer study and the AIM study were considered to be at high risk of bias because of methods of imputation and exclusion of non-adherent patients from analyses, respectively.	Comment noted.

Commentator	Comment	Response
CSAS	Safety: There was no significant difference between abatacept (10mg/kg) and placebo in rates of serious adverse events at 6 or 12 months. Abatacept was associated with lower rates of serious adverse events, lower discontinuation rates and lower rates of both serious infections and acute infusional events than infliximab.	The Committee noted that these comments referred to a recently published network meta-analysis and Cochrane overview, which reported that abatacept was amongst the biological DMARDs for which no increased rate of side effects compared with placebo had been proven in the short term, whereas for others an increased rate was shown. However, the authors of the report expressed caution with interpreting these results because there was no consistency across the outcomes, and concluded that people who take biological DMARDs will probably experience more side effects or drop out of the study due to side effects than people who take placebo. The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus methotrexate. (see FAD section 4.10)

Commentator	Comment	Response
CSAS	Cost effectiveness: The Appraisal Committee considered a model submitted by the manufacturer, based on cost utility analyses over a lifetime horizon and from the healthcare provider prospective in which abatacept was compared with conventional DMARDs, all other biological DMARDs, and infliximab plus methotrexate. Abatacept and infliximab were dominated by adalimumab and certolizumab pegol in patients who could receive a subcutaneous injection. In patients who could not receive a subcutaneous injection, infliximab was extendedly dominated by abatacept and a conventional DMARD at a cost per QALY of £29,888 compared with conventional DMARDs alone. Although the ICER for abatacept is below the accepted threshold of cost effectiveness used for NHS therapies, some of the key assumptions were of concern to the ERG, and the Appraisal Committee felt that the concerns about the base case of the model were important and that plausible ICERs would in fact be greater than £30,000 per QALY. Specific concerns related to the methodological quality and presentation of the economic evaluation were: • The model was more complex than most seen previously by the ERG. • The use of HAQ scores instead of DAS-28, the mapping of HAQ scores to EQ-5D utility values, failure to include patient disutility in attending for infusions and assumptions around how disease progresses on and off different treatments. • Structurally the model did not allow the use of multiple biological DMARDs and did not therefore reflect current UK practice. • In the base case, the model did not allow dose escalation with abatacept although this had been included for infliximab and etanercept. • The model did not allow for vial sharing of infliximab. Many of the assumptions made by the manufacturer in modeling favoured abatacept. ICERs from modeling with more 'realistic assumptions' (according to the ERG or in the manufacturer's sensitivity analyses) always increased to above £29,700 per QALY. In particular, sensitivity analyses demonstrated a large effect of the time horizon. The time horizon in the manufacturer's base case was the lifetime and sensitivity analyses demonstrated that changing this to five years had a large effect on the ICER, changing it from £29,900 per QALY gained in the manufacturer's base case to £84,400. Overall the ACD concluded that a model that combined plausible assumptions would produce ICERs that exceeded the range that represented an effective use of NHS resources.	Comment noted.

Commentator	Comment	Response
CSAS	Additional factors: • The manufacturer indicated that denying intravenous treatment to people who require/request it on the grounds of age, disability or ethnic race would be unfair. The Committee considered that many of the patients who were identified in the submission as being unsuited to subcutaneous pharmacotherapy would be able to receive subcutaneous therapy administered by nursing personnel in the home. As a result, the ACD concluded that the manufacturer's definition of this group was not relevant for clinical practice in the UK and that this did not present an equality issue. • The ACD acknowledges the importance of choice for people who have inadequate response to initial DMARD treatment, and accept that the choice of a biological with a mechanism of action other than TNF inhibition may be important for people who cannot take these drugs.	Comment noted.
MSD	Section 3.9 states that in the Kremer phase 2b and AIM trials, abatacept plus methotrexate led to statistically significant improvements from baseline in the physical and mental components of the SF-36 at 6 months compared with placebo plus methotrexate. We would kindly suggest that it is also noted here that from Kremer phase 2b trials the mental component score for abatacept 2 mg/kg plus methotrexate at one year was not statistically significant.	Comment noted. Abatacept is currently licensed at a dose of approximately 10 mg/kg. The Committee is unable to make recommendations about the use of technologies outside of their current marketing authorisation. (See section 6.1.8 of the NICE methods guide).

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<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>Section 3.38
MSD supports the preference of the ERG for the hybrid analysis and agrees that 63% represents the vial sharing that occurs with infliximab.
As costs are an integral component of all economic evaluations, it is important that they are estimated as accurately and consistently as possible across Technology Appraisals and reflect NICE’s objectives with respect to issuing national guidance (Decision Support Unit Briefing Paper on Costs, A Miners, 2007). Given that vial wastage may have a substantial impact in estimating cost-effectiveness, it is appropriate for NICE to make recommendations that take account of vial sharing.
In their original manufacturer submission (MS), Bristol Myers Squibb (BMS) did not allow for vial sharing for infliximab. MSD feel that this acts to bias results in favour of abatacept and argue that, in line with the ERG□s □Hybrid analysis□, there should be at least 63% vial sharing included for Infliximab in the basecase submission for abatacept.
The value of 63% comes from a study which contacted rheumatology pharmacists and nurses nationwide to determine typical clinical practice for vial sharing. 162 centres were contacted to ask the following vial sharing questions:
(1) Do you vial share with infliximab in rheumatology?
(2) What proportion of rheumatology patients received doses of infliximab treatment which have been vial optimised?
The results of these questions were then compiled and analysed to determine the proportion of patients responding to the questionnaire that were vial sharing.
Of the 162 centres contacted, 33% (n=54) responded to the question:
<table>
<tr><th>Number of Patients</th><th colspan="2">Number of Centres</th><th>% of total number of patients</th></tr>
<tr><td>Yes</td><td>2,047</td><td>19</td><td>63.04%</td></tr>
<tr><td>No</td><td>1,200</td><td>35</td><td>36.96%</td></tr>
<tr><td>Total</td><td>3,247</td><td>54</td><td>100.00%</td></tr>
</table>
MSD therefore strongly urges that evidence from clinical specialists regarding vial sharing be taken into account by NICE in this appraisal and that the Appraisal Committee will take a similar and consistent approach to the issue of vial wastage as that in previous appraisals (TA133[a], TA195[b]).</td><td>Comment noted. The Committee concluded that the question of the cost effectiveness of abatacept plus methotrexate compared with infliximab plus methotrexate for the population of people for whom self-administration of subcutaneously-injected biological agents is unsuitable is not relevant for the NHS. (see FAD section 4.13).

The Committee noted that in all individual comparisons, abatacept plus methotrexate was dominated by subcutaneous therapies. The Committee agreed with the manufacturer that, compared with subcutaneously-injected biological DMARDs, abatacept plus methotrexate would not provide a cost-effective use of NHS resources. (see FAD section 4.12).</td></tr>
</table>

Commentator	Comment	Response
MSD	In table B80 the dose description for golimumab is incorrectly stated as 50 mg every four weeks. The correct wording from the SmPC for golimumab is 50 mg given once a month on the same date each month.	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	I agree with the Appraisal Committees preliminary recommendations	Comment noted.
NHS professional 1	3	I believe the manufacturers comments and cost modelling in relation to patients who cannot self inject is flawed in that in such situations, other means of injection for subcutaneous preparations are available either through other carers being trained, or via nurse administration. Cost modelling in relation to cost effectiveness of abatacept are also flawed in relation to real life use of DMARDs and biologics, including vial sharing etc. by applying limitations within the manufacturers cost model the model favours abatacept. If real life use of biologic and non biologic DMARDs are considered I do not believe abatacept to be a cost effective use of NHS resources for this indication. The trial information used to assess effectiveness of abatacept vs other biologics is not robust - trials used have patients with differing baseline characteristics, which makes it difficult to assess the true efficacy of the comparator treatments (five different biologics). I agree with the comments made by the evidence review group in relation to omitted trial data, and inconsistent presentation of data, and omissions of data from key trials.	The Committee heard that subcutaneous interventions could be administered at home by a nurse or a family member, subject to local decision-making, or in hospitals (as with intravenous infusions), where clinicians could monitor people more closely if required. The Committee concluded that people with needle phobia are likely to have a similar problem with intravenous therapy, and if necessary could possibly be assisted by a nurse or family member. The Committee was aware that psychological treatments for needle phobias and aversion exist. It agreed that there was no clinically plausible reason related to route of administration that supports limiting the decision problem to this population. The Committee concluded that the question of the cost effectiveness of abatacept plus methotrexate compared with infliximab plus methotrexate for people for whom self-administration of subcutaneously-injected biological agents is unsuitable is not relevant for the NHS. (see FAD section 4.13). The Committee considered a consultation comment expressing the concern that one of the trials included participants whose disease had

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

Role*	Section	Comment	Response
			inadequately responded to conventional DMARDs other than methotrexate. Therefore the Committee viewed the results of the mixed treatment comparison with caution. (see FAD section 4.6).
NHS professional 1	4	I agree that abatacept plus methotrexate is not a cost effective use of NHS resource compared to subcutaneous biologic DMARDs based on the information provided. I agree with the view that the use of mortality estimates in relation to HAQ from old trials using older treatment modalities, is not in line with current practice, and is misleading re the relative benefits of Abatacept in relation to cost effectiveness. I agree with the recommendations of the appraisal committee. were abatacept to be given a positive appraisal, there would be considerable costs to the NHS, over and above those for other biologics in relation to the same patient cohort, not including additional costs for administration of an intravenous preparation - using abatacept would not be a cost effective sue of NHS resources.	Comment noted.
NHS professional 2	1	Is clearly written. Locally we do not anticipate our rheumatologists to disagree with this as we have not had any requests to fund this to date as an exceptional treatment	Comment noted.
NHS professional 2	3	How do you assess problems handling the injection devices, with mental health problems, or with an aversion to, or phobia of, needles. Can see more than 10% patients not wanting to inject themselves.	The Committee heard that subcutaneous interventions could be administered at home by a nurse or a family member, subject to local decision-making, or in hospitals (as with intravenous infusions), where clinicians could monitor people more closely if required. The Committee concluded that people with needle phobia are likely to have a similar problem with intravenous therapy, and if necessary could possibly be assisted by a nurse or family member. The Committee was aware that psychological treatments for needle phobias and aversion exist. It agreed that there was no clinically plausible reason related to route of administration that supports limiting the decision problem to this

Role*	Section	Comment	Response
			population. The Committee concluded that the question of the cost effectiveness of abatacept plus methotrexate compared with infliximab plus methotrexate for people for whom self-administration of subcutaneously-injected biological agents is unsuitable is not relevant for the NHS. (see FAD section 4.13).
NHS professional 3	-	Uncertainties about the effectiveness of abatacept in this indication remain. Â Although direct evidence showed that abatacept plus methotrexate is more effective than placebo plus methotrexate, the manufacturer?s mixed treatment comparison that compared the combination with five biological DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) plus methotrexate, was viewed with caution by the Appraisal Committee because it omitted key trials and included trials of participants with different baseline characteristics. 3) Abatacept is not considered to be a cost effective use of NHS resources when realistic assumptions are made. The Committee had concerns about the quality and presentation of the manufacturer?s economic model, in particular: Â the mapping of HAQ scores to EQ-5D utility values failure to include patient disutility in attending for infusions assumptions around how disease progresses on and off different treatments not reflecting current practice where multiple DMARDs may be used not allowing for dose escalation with abatacept not allowing for vial sharing for infliximab and using a lifetime time horizon. A model that relied on a combined set of more plausible assumptions is expected to produce an ICER greater than Â£29,700, which exceeds the range considered to represent an appropriate use of NHS resources (Â£20-30,000 per QALY or more). 3) The Appraisal Committee did not accept the manufacturer?s suggested focus on the population subgroup who cannot self-inject. In addition to the main population and comparison (the decision problem) described in the scope, the manufacturer?s submission focused on the Â use of intravenous abatacept as an alternative to intravenous infliximab for people with rheumatoid arthritis who	Comment noted.

Role*	Section	Comment	Response
		experience an inadequate response to traditional DMARDs and for whom a self-administered subcutaneous administered biological agent is not suitable. The Evidence Review Group (ERG) noted that many of the patients who were identified in the submission as being unsuited to subcutaneous pharmacotherapy would be able to receive subcutaneous therapy administered by nursing personnel in the home. As a result, the Appraisal Committee concluded that the question of cost-effectiveness of abatacept versus infliximab (plus methotrexate) for this subgroup was irrelevant for the NHS.	
NHS professional 3	4	The included trials found no significant difference between abatacept (10mg/kg) and placebo in rates of serious adverse events at 6 or 12 months. Abatacept was associated with lower rates of serious adverse events, lower discontinuation rates and lower rates of both serious infections and acute infusional events than infliximab.	The Committee noted that these comments referred to a recently published network meta-analysis and Cochrane overview, which reported that abatacept was amongst the biological DMARDs for which no increased rate of side effects compared with placebo had been proven in the short term, whereas for others an increased rate was shown. However, the authors of the report expressed caution with interpreting these results because there was no consistency across the outcomes, and concluded that people who take biological DMARDs will probably experience more side effects or drop out of the study due to side effects than people who take placebo. The Committee understood that the trial data presented to Committee showed that overall adverse event rates were similar for abatacept plus methotrexate and placebo plus methotrexate. However, the Committee was also aware that it had not been presented with comparative long-term adverse event data. The Committee considered that adverse events would be expected to occur with abatacept plus methotrexate more frequently over time than with placebo plus methotrexate. The Committee concluded that in the absence of any long-term comparative adverse event data being presented, there was uncertainty about differences over time in adverse events with abatacept plus methotrexate compared with placebo plus

Role*	Section	Comment	Response
			methotrexate. (see FAD section 4.10)
NHS professional 4	1	Abatacept should be reserved for patients who fail other biologics or wheree these are contradicated.	When TNF inhibitors are contraindicated (congestive heart failure) and etanercept is considered unsuitable because of congestive heart failure, an ICER would likely to be much higher than what is normally considered to be an appropriate use of NHS resources, but because of the lack of evidence it is not possible to refer to a precise figure. More importantly, the Committee did not consider it appropriate to provide a separate recommendation for the use of a technology in a group of people for whom no evidence of clinical benefit was available, whose health status is not comparable to the overall trial population, who have very complex medical needs, and where any decision on the use of biological treatments would require a careful balance of the potential benefits and harms for the individual patient. (see FAD section 4.18 and 4.20)
NHS professional 4	2	Rather expensive treatment. It may be worth negotiating discounts with the manufacturer.	Comment noted.