NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125)

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

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Pfizer (was Wyeth Pharmaceuticals)</td><td>Pfizer is pleased that the Appraisal Committee (AC) after due consideration of the evidence submitted and the views of the manufacturer consultees, commentators, clinical and patient experts has produced a positive preliminary recommendation for etanercept for the treatment of psoriatic arthritis.</td><td>Comment noted. No action required.</td></tr>
<tr><td>Pfizer</td><td>In particular, we welcome the AC comments in Section 4.3.3 on p22 that etanercept is a clinically effective treatment for psoriatic arthritis
“The Committee considered the clinical effectiveness data presented by the manufacturers and noted that etanercept, infliximab and adalimumab all showed a statistically significant response in the joint disease (PsARC, ACR) and skin disease (PAS) at 12- and 24- week follow-up compared with placebo.”</td><td>Comment noted. No action required.</td></tr>
<tr><td>Pfizer</td><td>Pfizer also welcomes the AC conclusions in Section 4.3.10, p26 that etanercept represents a cost-effective treatment for psoriatic arthritis.
“..the Committee considered that the evidence on clinical and cost-effectiveness for etanercept and adalimumab was not sufficient to allow a choice to be made between one drug over the other, and was aware that they both represented a cost-effective use of NHS resources, with equivalent acquisition and administration costs. The Committee considered that the criteria for recommending etanercept (in NICE technology appraisal guidance 104) and adalimumab (in NICE technology appraisal guidance 125) remained valid.”</td><td>Comment noted. No action required.</td></tr>
<tr><td>Pfizer</td><td>Overall, Pfizer agrees that all the relevant evidence for etanercept has been taken into account and that the summaries of the clinical and cost effectiveness for etanercept have been interpreted in an appropriate manner within the ACD with the result that the provisional recommendations are sound and a suitable basis for guidance to the NHS.</td><td>Comment noted. No action required.</td></tr>
<tr><td>Pfizer</td><td>However, we have two comments relating to the ACD. The first relates to the statement included in Section 4.1.2 of the ACD that data for etanercept on PASO at week 12 were available from the MEASE 2000 trial only. This is not correct as we included in our submission pooled data from Mease 2000 and Mease 2004. Please see attached table of the pooled results.
Pooled estimates of PASI response – outcomes at 12 weeks
<table>
<tr><td></td><td>PASI 75</td><td></td><td></td><td></td></tr>
<tr><td>Mease 2000</td><td></td><td>5/19 (26%)</td><td>0/19 (0%)</td><td>11.00 (0.65, 186.02) p=0.046</td></tr>
<tr><td>Mease 2004</td><td></td><td>8/66 (12%)</td><td>5/62 (8%)</td><td>1.50 (0.52, 4.35) p=0.563</td></tr>
<tr><td></td><td>Pooled RR (95% CI), p
P for heterogeneity</td><td>13/85 (15%)</td><td>5/81 (6%)</td><td>2.34 (0.91, 6.03) p=0.078
P=0.18</td></tr>
</table></td><td>Comment noted.
The manufacturer of etanercept original submission did not include the PASI response at 12 weeks. This new data has not been reviewed by the Assessment Group or considered by the Committee in the final guidance.</td></tr>
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<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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<table>
<tr><td></td><td>PASI 50</td><td></td><td></td><td></td></tr>
<tr><td>Mease 2000</td><td></td><td>8/19 (42%)</td><td>4/19 (21%)</td><td>2.00 (0.72, 5.53) p=0.295</td></tr>
<tr><td>Mease 2004</td><td></td><td>24/66 (36%)</td><td>9/62 (15%)</td><td>2.50 (1.26, 4.96) p=0.008</td></tr>
<tr><td></td><td>Pooled RR (95% CI), p
P for heterogeneity</td><td>32/85 (38%)</td><td>13/81 (16%)</td><td>2.35 (1.33, 4.15) p=0.003
P=0.72</td></tr>
</table>
</td><td></td></tr>
<tr><td>Pfizer</td><td>The second comment relates to the statement included in Section 3.4, p6 of the ACD stating that the manufacturer of Infliximab is Wyeth Pharmaceuticals. This statement is not correct as Infliximab is manufactured by Schering Plough.</td><td>Comment noted. FAD amended accordingly.</td></tr>
<tr><td>Abbott</td><td>Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of adalimumab, etanercept and infliximab for the treatment of psoriatic arthritis. Abbott's comments are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.</td><td>Comment noted. No action required.</td></tr>
<tr><td>Abbott</td><td>1. Has all of the relevant evidence been taken into account?
Abbott is not aware of any relevant evidence that has not been taken into account when the Committee was making its preliminary recommendations.</td><td>Comment noted. No action required.</td></tr>
<tr><td>Abbott</td><td>2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Abbott considers that the summaries of clinical and cost-effectiveness are mostly reasonable interpretations of the evidence, however Abbott considers that the evidence supports that adalimumab and infliximab are more effective at treating the skin component of the disease than etanercept. This is in accordance with the conclusions of Heiberg et al[i]. "Although no head to head comparisons have been performed between the different TNF-blocking agents, similar magnitude of clinical response has been observed across trials with the different agents with respect to joint symptoms, whereas improvements in skin manifestations seem to be somewhat greater with the monoclonal antibodies." This is also supported by the lower levels of PASI response estimated for etanercept compared to adalimumab and infliximab in indirect comparisons conducted for NICE appraisals in patients with plaque psoriasis[ii,iii].</td><td>Comment noted.
The Committee noted that each of the TNF inhibitors showed a statistically significant response for the joint and skin components of the disease. The Committee considered the evidence in light of advice from the clinical experts and concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of individual TNF inhibitors in the treatment of psoriatic arthritis. See FAD section 4.3.3.</td></tr>
<tr><td>Abbott</td><td>3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
Abbott considers that the provisional recommendations are sound and constitute a suitable basis for the preparation of guidance to the NHS.</td><td>Comment noted. No action required.</td></tr>
<tr><td>Abbott</td><td>4. Are there any aspects of the recommendations that need particular</td><td>Comment noted. No action required.</td></tr>
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Consultee	Comment	Response
	consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None that Abbott is aware of.	
Abbott	References Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, Kvien TK. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6- month results from a longitudinal, observational, multicenter study. Ann Rheum Dis. 2007 Aug;66(8):1038-42 National Institute for Health and Clinical Excellence. Adalimumab for the treatment of adults with psoriasis. TA146 June 2008. National Institute for Health and Clinical Excellence. Infliximab for the treatment of adults with psoriasis. TA134 January 2008.	Comment noted. No action required.
Schering-Plough	Schering-Plough welcomes the opportunity to comment on ACD for the appraisal of TNF-α inhibitors in psoriatic arthritis. Following a thorough review of the ACD and the accompanying amendments to The CRD/CHE Technology Assessment Group (TAG) analysis, this letter sets out Schering-Plough's comments – a summary of what we perceive to be the shortcomings of the TAG analysis and the resultant significant findings for infliximab which we believe the Appraisal Committee (the Committee) should consider.	Comment noted. No action required.
Schering-Plough	1 Inappropriate consideration of evidence 1.1 Incomplete presentation of evidence on infliximab The calculations of the treatment costs of TNF-α inhibitors presented by the TAG in their original technology assessment report (TAR) (Table 10.13.3; Page 329) and the amendment following the Committee meeting (Table 10.13.3) seem to suggest that the TAG conducted two separate analysis with a mean of 3 or 4 vials of infliximab for up to 60kg and 70-80kg patient body weight with no vial sharing. However, TAG has only presented the results for the 70-80kg patients with no vial sharing in the base case and restricted the 60kg patient scenario as a sensitivity analysis in TAR. No such analysis was presented in the amendment dated 23rd February 2010, after the costs for adalimumab and etanercept were corrected.	Comment noted. During consultation on the ACD the manufacturer of infliximab presented additional evidence on the cost effectiveness of the TNF inhibitors which incorporated vial sharing with infliximab treatment. The Committee did not consider that there was a robust way in which vial sharing could be incorporated in to the model but accepted that vial sharing would reduce the cost and ICER of infliximab compared to etanercept and adalimumab. The Committee therefore concluded that all three anti TNF inhibitors be recommended and that the treatment choice should be based on cost, taking

Consultee	Comment	Response
		into account any local discounting agreements and/or vial-sharing arrangements. See FAD sections 1.1, 1.2 and 4.3.7.
Schering-Plough	The Committee's request for further sensitivity analyses seems to suggest the Committee's acknowledgment of comparable efficacy between adalimumab and etanercept, and superior efficacy of infliximab (ACD section 4.3.9). Schering-Plough therefore believes that for the PsA patients requiring infliximab dosing of 3 vials per infusion, infliximab is a cost effective treatment option over and above adalimumab and etanercept (ICER = £8,377/QALY compared to subcutaneous TNF-α inhibitors) and should therefore be recommended.	Comment noted. Following consideration of consultee comments (including the effect of vial sharing with infliximab on the ICERs) on the ACD the Committee recommended all three anti-TNF inhibitors. The treatment choice should be based on cost, taking into account any local discounting agreements and/or vial-sharing arrangements. See FAD sections 1.1, 1.2 and 4.3.7.
Schering-Plough	Schering-Plough therefore urges the Committee to reconsider their guidance and recommend the TNF-α inhibitor with cheapest acquisition cost depending on local arrangements to be used in practice. This is in accordance with the precedent set in the most recent appraisal of TNF-α inhibitors in Crohn's disease wherein the Committee allowed equal access to all the available TNF-α inhibitors and recommended the use of TNF-α inhibitor with the cheapest treatment cost including cost of administration.	Comment noted. Following consideration of consultee comments (including the effect of vial sharing with infliximab on the ICERs) on the ACD the Committee recommended all three anti-TNF inhibitors. The treatment choice should be based on cost, taking into account any local discounting agreements and/or vial-sharing arrangements. See FAD sections 1.1, 1.2 and 4.3.7.
Schering-Plough	1.2 No consideration of vial optimisation for infliximab Vial optimisation with infliximab has significant implications on the resulting ICERs. The TAG did not consider vial optimization in their analysis, even as part of sensitivity analysis. A recent survey of rheumatology centres across England and Wales suggested that 63% of all rheumatology patients undertake vial optimisation and a minimum of 50% of drug wastage is avoided in centres that undertake vial optimisation.	Comment noted. Following consideration of consultee comments (including the effect of vial sharing with infliximab on the ICERs) on the ACD the Committee recommended all three anti-TNF inhibitors. The treatment choice should be based on cost, taking into account any local discounting agreements and/or vial-sharing arrangements. See FAD sections 1.1, 1.2 and 4.3.7.

Consultee	Comment	Response
Schering-Plough	Vial optimisation has also been considered in other appraisals. In a previous appraisal for an asthma medication, omalizumab, the Committee has considered vial optimisation while issuing their guidance (Technology Appraisal 133). Paragraph 4.12 of TA 133 states: "The Committee considered the basis for estimating omalizumab drug costs in the manufacturer's model. It noted that this had been done on a per-mg basis (assuming no wastage and reuse of unused vial portions) and that in scenarios in which omalizumab drug costs were estimated on a per-vial basis, the ICERs for omalizumab were higher. It was mindful that vial sharing might not be feasible in primary care settings. However, the Committee heard from patient experts and clinical specialists that vial wastage could be avoided reasonably easily in regional specialist centres where larger numbers of patients are treated. The Committee therefore concluded that the ICERs for omalizumab in comparison with standard therapy may be lower when omalizumab is administered in a dedicated session in a specialist day care setting where vial wastage can be minimised."	Comment noted. Following consideration of consultee comments (including the effect of vial sharing with infliximab on the ICERs) on the ACD the Committee recommended all three anti-TNF inhibitors. The treatment choice should be based on cost, taking into account any local discounting agreements and/or vial-sharing arrangements. See FAD sections 1.1, 1.2 and 4.3.7.
Schering-Plough	As infliximab is administered within specialist centres, it may be reasonably assumed that vial optimisation may be applicable. Indeed, the ongoing NICE appraisal of infliximab for the treatment of Crohn's disease recently released an Appraisal Consultation Document which stated that local vial sharing arrangements should be taken into account in the consideration of which treatment should be administered.	Comment noted. Following consideration of consultee comments (including the effect of vial sharing with infliximab on the ICERs) on the ACD the Committee recommended all three anti-TNF inhibitors. The treatment choice should be based on cost, taking into account any local discounting agreements and/or vial-sharing arrangements. See FAD sections 1.1, 1.2 and 4.3.7.
Schering-Plough	2 Significant findings for infliximab The indirect comparison results from the TAG analysis suggested that infliximab is consistently superior to etanercept and adalimumab on all of the treatment outcomes. This was most evident on psoriasis outcomes and among patients with significant psoriasis. Although the results did not reach statistical significance this could be attributed to underpowering of the clinical trials on psoriatic outcomes. The feedback from the clinical experts during the Committee meeting also suggested a wider clinical view that infliximab is a superior TNF-α inhibitor in psoriasis. The superiority of infliximab in psoriasis has already been acknowledged in a previous appraisal (TAG 134; Pages 12-13) and has been recommended based on its superior clinical outcomes. Schering-Plough therefore urges the Committee to view following cost effectiveness results in this context and allow unrestricted use of infliximab at least for patients with significant psoriasis.	Comment noted. The Committee considered the clinical-effectiveness data presented by the manufacturers and noted that etanercept, infliximab and adalimumab all showed a statistically significant response in the joint disease (PsARC, ACR) and skin disease (PASI) criteria at 12-week and 24-week follow-up compared with placebo. The Committee heard from the clinical specialists that there was no theoretical reason to believe that the TNF inhibitors would differ in their efficacy in treating

Consultee	Comment	Response
		psoriatic arthritis. It heard that etanercept, infliximab and adalimumab were similarly effective in the treatment of psoriatic arthritis in clinical practice, and were used interchangeably. Although the indirect comparison conducted by the Assessment Group suggested that infliximab is the most effective treatment overall, taking into account both skin and joint disease, the Committee concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of individual TNF inhibitors in the treatment of psoriatic arthritis (se FAD section 4.3.3). The Committee also considered the subgroup of people for whom treatment with TNF inhibitors yields a PASI 75 response but not a PsARC response. The Committee concluded that people whose skin disease achieves a PASI 75 response but whose psoriatic arthritis does not achieve an adequate PsARC response should be assessed by a dermatologist to determine whether continued treatment with etanercept, adalimumab or infliximab is indicated for the treatment of the psoriatic component of the condition alone. See FAD section 4.3.9.

Consultee	Comment	Response
Schering-Plough	2.1 Treatment of choice for patients with significant psoriasis The TAG concludes that among PsA patients with moderate to severe psoriasis, if the response is defined as PsARC or PASI 75 then infliximab has the highest probability of being cost effective at a threshold of £30,000 per QALY. If a higher threshold of PsARC and PASI response is used then infliximab has the highest probability of being cost effective at both £20,000 per QALY and £30,000 per QALY thresholds. 2.2 Treatment of choice for patients requiring inpatient treatment The TAG also concludes that for uncontrolled moderate to severe psoriasis patients requiring inpatient treatment infliximab is likely to be the most cost effective strategy at a threshold of £20,000 per QALY.	Comment noted. The Committee considered the subgroup of people for whom treatment with TNF inhibitors yields a PASI 75 response but not a PsARC response. The Committee concluded that people whose skin disease achieves a PASI 75 response but whose psoriatic arthritis does not achieve an adequate PsARC response should be assessed by a dermatologist to determine whether continued treatment with etanercept, adalimumab or infliximab is indicated for the treatment of the psoriatic component of the condition alone. See FAD section 4.3.9.
Schering-Plough	In summary, Schering-Plough urges the Committee to consider infliximab's superior efficacy on all outcomes and its significant benefit to 'difficult to treat' PsA patients with moderate to severe psoriasis whilst recommending the TNF-α treatment. Once again, we are grateful for the opportunity to comment on the TAR and look forward to continued dialogue with NICE regarding the issues raised in this response.	Comment noted. The Committee concluded that etanercept, infliximab and adalimumab should be recommended as treatment options for people with psoriatic arthritis with three or more affected joints whose disease had inadequately responded to at least two conventional DMARDs and that the choice of treatment should be based on cost, taking into account acquisition and administration costs and any local discounting agreements and/or vial-sharing arrangements.
Schering-Plough	References: NICE Final Appraisal Determination (TA 133), Omalizumab for severe persistent allergic asthma, August 2007, available at http://www.nice.org.uk/nicemedia/pdf/FADOmalizumabAsthma.pdf. NICE. Crohn's Disease: Infliximab and adalimumab. Appraisal Committee Document. Section 4.3.11. Available from: http://www.nice.org.uk/guidance/index.jsp?action=folder&o=46233	Comment noted. No action required.
Department of	Thank you for the opportunity to comment on the appraisal consultation document for the	Comment noted. No action required.

Consultee	Comment	Response
Health	above health technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment. Please note that we have no comments to submit at this stage.	Comment noted. No action required.
Royal College of Nursing	The Royal College of Nursing was invited to comment on the Appraisal Consultation Document (ACD) of the technology appraisal of etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (review). Nurses caring for these patients reviewed this document on behalf of the RCN. The RCN welcomes the opportunity to comment on this document and responds below to the four questions on which comments were requested:	Comment noted. No action required.
Royal College of Nursing	Appraisal Consultation Document – RCN Response The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (review). The RCN's response to the four questions on which comments were requested is set out below: i) Has the relevant evidence been taken into account? We would commend the summary of the evidence in this document. It is, however, unclear where guidance on treating skin symptoms and or joint symptoms overlap or how guidance for treating psoriasis would fit with this appraisal.	Comment noted. This is an appraisal of etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis which includes the joint and skin components of the disease.
Royal College of Nursing	ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate? We do not have the expertise to comment on the full economic modelling for this appraisal. However, in the estimates of quality of life, we could not determine any mention of depression. Depression is much more prevalent in patients with psoriatic arthritis and can have a significant adverse effect on quality of life.	Comment noted. The Committee noted that depression is a component of EQ-5D in the health related quality of life evaluation recommended in the NICE reference case. It considered that psychological effects had been indirectly, if not specifically, captured in the modelling.
Royal College of Nursing	iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? The provisional recommendations of the Appraisal Committee seem a suitable basis for preparation of guidance to the NHS.	Comment noted. No action required.
Royal College of	iv) Are there any equality related issues that need special consideration that are not	Comment noted. No action required.

Consultee	Comment	Response
Nursing	covered in the ACD? At present we do not know if certain groups of patients (e.g. ethnic minority or other specific genetic patient groups) would have benefited from such a treatment. There do not appear to be any equality issues that have been missed otherwise at this stage.	
The Psoriasis and Psoriatic Arthritis Alliance (PAPAA)	Thank you for the opportunity to comment on the ACD for the above appraisal. As these technologies are expensive we welcome the committee's decision to continue to recommend these treatments as being cost effective for use in people affected by psoriatic arthritis.	Comment noted. No action required.
PAPAA	With regard to the specific questions, we believe that: The summaries of clinical and cost effectiveness reasonable interpretations of the evidence The provisional recommendations are sound and a suitable basis for guidance to the NHS	Comment noted. No action required.
PAPAA	We don't believe that there are any aspects of the recommendations that need particular consideration to avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? Although, I have some concerns with section 6 for further research. it says: "...6 proposed recommendations for further research. 6.1 The Committee was aware of the importance of collecting further data within registries including patients receiving biologic treatments for psoriatic arthritis to enable the collection of information on long-term outcomes including adverse events..." Which although laudable, doesn't mean very much, if such data isn't collected in a methodical manner. Therefore, it occurs to me that there is some inequity for people who only have psoriatic arthritis when prescribed biologics. No data appears to be gathered in a registry for outcomes and adverse events as is the case for psoriasis, rheumatoid arthritis and the soon to be started ankylosing spondylitis registry.	Comment noted. The Committee noted the comments from clinical specialists about the benefits of having combined input from rheumatologists and dermatologists in managing this multisystem disease. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about these treatments in psoriatic arthritis can be captured. See FAD section 4.3.9 and 4.3.11.
PAPAA	For the recent TA180 ustekninumab for psoriasis appraisal the recommendation section says: "..6 Recommendations for further research 6.1...The Committee considered that the following research would be of value: The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR)..." Although, the BADBIR collects data on patients who have co-existing inflammatory arthritis but not specifically psoriatic arthritis; the Health Assessment Questionnaire is collected from all	Comment noted. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable

Consultee	Comment	Response
	patients with co-existing inflammatory arthritis and also adverse event data on all the patients. No inflammatory arthritis specific disease activity or severity measures are included in the assessment and therefore are not collected.	registry so that specific information about these treatments in psoriatic arthritis can be captured. See FAD section 4.3.11.
PAPAA	In the appraisal for etanercept and efalizumab for the treatment of adults with psoriasis TA103 2006 6. Recommendations for further research, says: "6.2 … Procedures should be implemented to allow cross-referencing of BADBIR with information from people with PsA enrolled in the British Society for Rheumatology biologicals register…"	Comment noted. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about these treatments in psoriatic arthritis can be captured. See FAD section 4.3.11.
PAPAA	The British Society for Rheumatology Biologics Register (BSRBR) does collect data on psoriatic arthritis patients on biologics. The problem is that was a follow on from the rheumatoid arthritis database, so they collect DAS28 (inappropriate for psoriatic arthritis) and no data about skin at all. Ideally this needs to change and some meaningful outcome measures need to be collected for the psoriatic arthritis patients. It would appear to me that the importance of long-term observational registers in trying to identify subgroups of patients who are more likely to respond to these drugs, would be extremely useful, particularly for future reviews and appraisals of new technologies. I think from a patient perspective the collection of appropriate data including adverse events and meaningful outcome end points for people who are taking these drugs and who only have psoriatic joint involvement would be very useful. A stronger or possibly mandated recommendation from NICE would make this more likely to happen, and provide much more robust data than might otherwise be available in the future.	Comment noted. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about these treatments in psoriatic arthritis can be captured. See FAD section 4.3.11.
PAPAA	Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis TA36 2002 (Page 15) says: "…The doctor who prescribes etanercept or infliximab for you should, with your consent, register you with the Biologics Registry, which has been set up by the British Society for Rheumatology. Every 6 months, the doctor will send information to the Registry on the drug you are receiving, the effects of the treatment and any side effects you have experienced. This information will help researchers to find out about the long-term effectiveness and side effects of treatment with etanercept and infliximab…"	Comment noted. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about

Consultee	Comment	Response
		these treatments in psoriatic arthritis can be captured. See FAD section 4.3.11.
PAPAA	Would the committee consider inserting such an assertion into this guidance along the following lines? ...The Committee was aware of the importance of collecting further data within registries including patients receiving biologic treatments for psoriatic arthritis to enable the collection of information on long-term outcomes including adverse events. In future a dedicated psoriatic arthritis data set or registry should be setup similar to those for psoriasis and rheumatoid arthritis as set up by the British Association of Dermatologist (BADBIR) and the British Society for Rheumatology (BSRBR)...	Comment noted. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about these treatments in psoriatic arthritis can be captured. See FAD section 4.3.11.
PAPAA	It would appear logical to me that it might be possible for those data to be collected via these existing registries, if appropriate outcomes were recorded, but I accept that NICE wouldn't be in a position to formally insist, as this would need to be appropriately discussed with the registry owners. Therefore, by mandating the need to collect data an appropriate solution might emerge, which collects data that is beneficial to current and future patients, when deciding on the risk benefits associated with biological therapies. Thank you for considering this suggestion.	Comment noted. The Committee was aware of registries that collect data for the long-term outcomes of treatment with TNF inhibitors for rheumatoid arthritis and psoriasis. The Committee noted the importance of registries in collecting data and supported including outcomes specific to psoriatic arthritis in a suitable registry so that specific information about these treatments in psoriatic arthritis can be captured. See FAD section 4.3.11.

Comments received from clinical specialists and patient experts

Patient expert	Comment	Response
Dr Ellie Korendowych	Thanks for forwarding the further information. I am happy with the result and would not have any further comments	Comment noted. No action required.

Patient expert	Comment	Response
Philip Helliwell **Leeds Institute of Molecular Medicine** **Section of Musculoskeletal Disease** **University of Leeds**	I have no further comments	Comment noted. No action required.

Comments received from commentators

Commentator	Comment	Response
NHS Quality Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? I note that this Appraisal Consultation Document on Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. As such it does not focus on conventional disease modifying therapy and omits golimumab. The inclusion of PASI scores in the economic analysis further complicates interpretation as the 2 processes are disconjugate in individual patients. The methodology differs from SIGN guidance where much of the data was obtained from meta-analysis and systematic reviews. The validity of the assessment group meta-analysis for NICE cannot be commented upon without further information.	Comment noted. As per the final scope for this appraisal (available via http://www.nice.org.uk/nicemedia/live/11966/40595/40595.pdf) golimumab was included as an intervention. Because of licensing issues it was not possible for NICE to appraise it with the other technologies. Also, as per the final scope, the population was defined as 'adults with active and progressive psoriatic arthritis who have responded inadequately to previous DMARDs'. The purpose of the appraisal was to focus on treatment with TNF inhibitors after failure of conventional DMARDs. NICE methodology is publicly available via the NICE website: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

Commentator	Comment	Response
NHS Quality Improvement Scotland	For etanercept the two studies referenced are Mease 2000 and Mease 2004. Recently Sterry et al BMJ 2010 have published on the PRESTA study comparing two different strategies for etanercept dosing. This is unlikely to have an impact on the conclusions of this document as the benefits were on speed of skin improvement rather than improvement in articular outcomes. Economic analysis is unlikely to prove favourable. Zachariae (Acta Derma Venereol 2008) also showed enhanced benefits of combination of methotrextae and etanercept on skin outcomes. In other studies this combination has not been shown to have enhanced effect on articular outcomes however may affect the assessment groups model of cost effectiveness. Although erosion scores were included in the clinical outcome for Mease etanercept and adalimumab studies, it is only in subsequent publications for infliximab (Van Der Heijde Ann Rheum Disease 2005;64 Suppl3:109) that the inhibition of erosions has been shown to be statistically significant. It could be interpreted that all three biologics inhibit erosions and therefore the omission of erosive scores in the economic analysis is unlikely to effect outcome.	Comment noted. The Assessment Group reviewed the manufacturer of etanercept submission, which included data from the PRESTA. The relationship between HAQ and EQ-5D observed in the PRESTA dataset was used in the base-case to generate utilities (see page 266 of the Assessment Report). The Committee considered the subgroup of people for whom treatment with TNF inhibitors yields a PASI 75 response but not a PsARC response. The Committee concluded that people whose skin disease achieves a PASI 75 response but whose psoriatic arthritis does not achieve an adequate PsARC response should be assessed by a dermatologist to determine whether continued treatment with etanercept, adalimumab or infliximab is indicated for the treatment of the psoriatic component of the condition alone. See FAD section 4.3.9. The Committee concluded that etanercept, infliximab and adalimumab were similarly effective. It concluded that etanercept, infliximab and adalimumab should be recommended as treatment options for people with psoriatic arthritis with three or more affected joints whose disease had inadequately responded to at least two conventional DMARDs and that the choice of treatment should be based on cost, taking into account acquisition and administration costs and any local discounting agreements and/or vial-sharing arrangements.
NHS Quality Improvement Scotland	2. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? The summaries of clinical and cost effectiveness seem reasonable given the above points.	Comment noted. No action required.

Commentator	Comment	Response
NHS Quality Improvement Scotland	3. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Many of the studies of anti-TNF agents enrolled patients who had disease activity less than that suggested by NICE and often they had not failed 2 standard disease modifying anti-rheumatic drugs (DMARDs) . This has been commented upon in the preliminary recommendation.	Comment noted. No action required.
NHS Quality Improvement Scotland	It was commented that the adverse event profile of anti TNF agents was comparable to that of conventional DMARDs yet no references were given for this statement. Withdrawal rates in studies using conventional DMARDs are often much higher than withdrawals from anti TNF agent studies. As such they may be said to have a worse toxicity to efficacy ratio.	Comment noted. The Committee heard from clinical specialists that the adverse event profile of TNF inhibitors was comparable to that of conventional DMARDs. It also heard that adverse events could result in a break from treatment, for example, by stopping treatment while an infection is resolved, then restarting. The Committee concluded that the tolerability profile of the three TNF inhibitors was comparable. See FAD 4.3.4.
NHS Quality Improvement Scotland	It is interesting that it is suggested that a trial of two conventional DMARDs are used prior to anti TNF agents. Again this statement doesn't have a particularly strong evidence base. Sulfasalazine and methotrexate were mentioned as DMARDs of choice. Up until recently there was very little evidence base for methotrexate and the data on sulfasalazine is very weak. Leflunomide is not mentioned despite it being mentioned in SIGN guidance. The evidence is lacking on the effectiveness of a second DMARD when the first has failed. This seems to be a pragmatic stance to limit economic impact and maintain a similarity with the guidance on rheumatoid arthritis. The pathways and treatment options do seem to be applicable to NHS Scotland perhaps with some debate over how many DMARDs should be tried before anti-TNF	Comment noted. NICE can only issue guidance according to the marketing authorisation. Full guidance on the NICE methodology on technology appraisals is available via: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf The previous guidance (TA104 and 125) which this review updates refers to the British Society or Rheumatology guidance on the use of anti TNF inhibitors for PsA which describes best practice on the use of these agents in the UK. The previous guidance considered this to be appropriate the recommended that the anti TNF therapy be initiated for people who have 'active joint disease (at least three tender joints and at least three swollen joints) and have failed to respond to adequate therapeutic trials of at least two standard DMARDs'. The Committee considered the appropriateness of this recommendation in the light of new evidence and concluded that the recommendation s of the previous guidance remained valid.

Commentator	Comment	Response
NHS Quality Improvement Scotland	4. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. No	Comment noted. No action required.
NHS Quality Improvement Scotland	5. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. No	Comment noted. No action required.
York Assessment Group	The Assessment Group (AG) welcomes the opportunity to comment on the ACD. Our comments fall into two main categories: 1) Inaccurate numerical estimates in the ACD. 2) Consideration of skin response to therapy. These are detailed below.	Comment noted. FAD amended where appropriate (see below)
York Assessment Group	1) Inaccurate numerical estimates in the ACD. Firstly, the AG noticed that several QALY and ICER values reported in the ACD were taken from a version of the AG report (4th December 2009) that has been superseded: following comments from consultees, the analyses in this report were revised and made available to NICE in advance of the Appraisal Committee meeting. Although the values in the revised analyses may not change the guidance, the AG feels these should be updated for the sake of accuracy. We have marked relevant changes in an accompanying document.	Comment noted. FAD amended accordingly.
York Assessment Group	Secondly, the 12-week PASI outcomes for the ADEPT trial mentioned in Section 4.1.12 are incorrect (the values reported in the ACD are 24-week data from this trial). We have corrected these values in the accompanying document.	Comment noted. FAD amended accordingly.
York Assessment Group	2) Consideration of skin response to therapy Psoriatic arthritis is a disease of the skin as well as the joints and in patients with significant skin disease its response to therapy should, if possible, be taken into consideration. Although Section 4.3.2 of the ACD correctly states that most RCTs were designed to detect an effect on joint disease (as measured by PsARC), the observed improvements in skin disease (as measured by PASI) are likely to be attributable to biologic therapy, as evidenced by the almost total lack of PASI 75 response among patients receiving placebo (e.g. Table 5.17 of the AG report).	Comment noted. The FAD indicates that all the agents have a beneficial effect on the skin as well as the joint disease.

Commentator	Comment	Response
York Assessment Group	The ACD guidance requires patients to withdraw from the initial biologic therapy if they do not achieve a PsARC response at 12 weeks. The evidence synthesis of the trial data suggests that a small proportion of patients (0% for etanercept but about 8-9% for infliximab and adalimumab) might achieve a response to PASI 75 but not achieve a PsARC response (Table 6.4 of AG report), and this is reflected in the decision model. The decision rule built into the base case of the decision model is that patients withdraw if they do not achieve a PsARC response, and this is reflected in the ACD guidance. However, a sensitivity analysis (number 35 in the revised cost-effectiveness analysis) finds that if patients are permitted to continue after 12 weeks if they achieve either a PASI 75 or a PsARC response then lifetime costs would be similar to the PsARC-only rule, but outcomes would be slightly superior. Therefore the model suggests that allowing patients to continue if they achieve either PsARC or PASI 75 is (slightly) more cost-effective than discontinuing for lack of PsARC response at 12 weeks.	Comment noted. The Committee considered the subgroup of people who achieved a PASI 75 response but not a PsARC response. The Committee concluded that people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.
York Assessment Group	The AG recognises that this conclusion is based on the assumptions that (a) patients who withdraw go to palliative care (ie no biologic) and (b) patients who do not achieve PsARC at 12 weeks would nevertheless receive some HAQ benefit and stop the progression of arthritis while on a biologic. These assumptions mean that, in the model, even a partial response on biologic is more effective and cost-effective than palliative care, as this is the only alternative. In reality, patients who do achieve PASI 75 but not PsARC may be better off withdrawing and trying another biologic, a scenario that the AG did not consider in the main analysis. Furthermore, the AG recognises that extending the continuation rule to include PASI 75 is only expected to affect a small proportion of patients. The majority of patients (80% or more from Table 6.4 of the AG) who have a PASI 75 response on biologic therapy would be expected also to have a PsARC response. The AG does not suggest that the guidance necessarily ought to be amended, but rather submit this response in order to check that psoriasis has been taken into account when drafting the ACD.	Comment noted. The Committee considered the subgroup of people who achieved a PASI 75 response but not a PsARC response. The Committee concluded that people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.

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York Assessment Group	The AG recognises that this conclusion is based on the assumptions that (a) patients who withdraw go to palliative care (ie no biologic) and (b) patients who do not achieve PsARC at 12 weeks would nevertheless receive some HAQ benefit and stop the progression of arthritis while on a biologic. These assumptions mean that, in the model, even a partial response on biologic is more effective and cost-effective than palliative care, as this is the only alternative. In reality, patients who do achieve PASI 75 but not PsARC may be better off withdrawing and trying another biologic, a scenario that the AG did not consider in the main analysis. Furthermore, the AG recognises that extending the continuation rule to include PASI 75 is only expected to affect a small proportion of patients. The majority of patients (80% or more from Table 6.4 of the AG) who have a PASI 75 response on biologic therapy would be expected also to have a PsARC response. The AG does not suggest that the guidance necessarily ought to be amended, but rather submit this response in order to check that psoriasis has been taken into account when drafting the ACD.	Comment noted. No Action required.

[i] Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, Kvien TK. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6- month results from a longitudinal, observational, multicenter study. Ann Rheum Dis. 2007 Aug;66(8):1038-42
[ii] National Institute for Health and Clinical Excellence. Adalimumab for the treatment of adults with psoriasis. TA146 June 2008.
[iii] National Institute for Health and Clinical Excellence. Infliximab for the treatment of adults with psoriasis. TA134 January 2008.