Adalimumab for the treatment of psoriatic arthritis

Erratum for Premeeting briefing and ERG report

After issuing the premeeting briefing and ERG report to the Appraisal Committee the following error was identified.

The manufacturer submission reported that utilities where calculated using M02-570 and data from another study (Table 6.2.6.1, page 68 in the manufacturer submission). The evidence review group (ERG) considered that this additional study involved patients with more severe disease leading to a potential over estimate of the impact of psoriasis on quality of life estimates in the model. The manufacturer clarified that these data had been used in an earlier version of the model, but were not utilised in the submitted version of the model and that reference to the use of these data was an error within their submission report.

This information was not included in the clarification response forwarded to the ERG and therefore not incorporated into the premeeting briefing and the ERG report. Statements on the use and potential effects of the additional study data are therefore retracted and should be disregarded in these documents.

Premeeting briefing:

- Page 3, 2nd bullet, 3rd subbullet
- Page 12, 5th bullet

ERG report:

- Page 66; section 5.3.7 (Health-related quality of life); paragraph 2, 3rd sentence
- Page 89; section 5.5.6 (Health-related quality of life); paragraph 1, 2nd through to 9th sentence.

End of erratum
Adalimumab for the treatment of psoriatic arthritis

Premeeting briefing

This briefing presents major issues arising from the manufacturer’s submission (MS), evidence review group (ERG) report and personal statements made by nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide two sets of clarification, one in December 2006 (1) and the other in January 2007 (2).

1. Three key areas:
   - effectiveness data
   - indirect/mixed treatment comparisons
   - economic analysis

2. The results of a re-run analysis, which excluded one non-controlled study of adalimumab.
Abbreviations

ACR American College of Rheumatology
AE adverse event
BSA body surface area
BSR British Society for Rheumatology
CI confidence interval
DLQI dermatology life quality index
DMARD disease-modifying anti-rheumatic drug
EQ-5D EuroQol-5D
FACIT functional assessment of chronic illness therapy
ERG evidence review group
HAQ health assessment questionnaire
ICER incremental cost-effectiveness ratio
MA marketing authorisation
MS manufacturer’s submission
NHS National Health Service
NSAID non-steroidal anti-inflammatory drug
PASI psoriasis area and severity index
PGA physician’s global assessment
PsA psoriatic arthritis
PsARC psoriatic arthritis response criteria
QALY quality-adjusted life year
RA rheumatoid arthritis
RCT randomised controlled trial
SF short-form [questionnaire]
SPC summary of product characteristics
TNF tumour necrosis factor
TSS total sharp score

Licensed indication

Adalimumab (Humira, Abbott Laboratories Ltd) is indicated for the treatment of active and progressive psoriatic arthritis (PsA) in adults when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.
Key issues for consideration

- Are the characteristics of the trial populations representative of the population currently being treated in UK clinical practice (that is, people with relatively severe PsA)?

- What effects do the following issues have on the credibility of the economic model
  - The efficacy estimates based on indirect comparisons rely on absolute response rates and one of the additional analyses produced counter-intuitive results.
  - The health assessment questionnaire (HAQ) progression used for the control arm was based on a value derived from people with severe PsA in palliative care, and the ‘rebound-to-gain’ assumption was used.
  - The utilities used were derived from, amongst other sources, people with severe PsA. Using alternative sources for the regression (SF-6D) resulted in much higher incremental cost-effectiveness ratios (ICERs).

- Does the Committee need to consider that the ICERs for the subgroup of people with PsA and skin involvement are lower than the ICERs for the subgroup of people with PsA without skin involvement?
## Decision problem

### Decision problem approach in the MS

<table>
<thead>
<tr>
<th>Population</th>
<th>The submission will address the clinical and cost effectiveness of treatment with adalimumab in accordance with the licensed indication outlined in the final scope. The SPC states ‘Humira is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate’.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Adalimumab (40 mg administered every other week as a single dose via subcutaneous injection)</td>
</tr>
</tbody>
</table>
| Comparators | Primarily:  
  - adalimumab versus conventional DMARDs  
  - etanercept versus conventional DMARDs  
  - infliximab versus conventional DMARDs.  
  Patients would most likely be given DMARDs such as leflunomide, methotrexate or sulphasalazine before anti-TNF-α treatment.  
  Secondary analysis compares adalimumab with other available biological therapies indicated for PsA (that is, etanercept and infliximab). |
| Outcomes | Impact of treatment on joint and skin components of the disease, including:  
  - ACR20/50/70 response  
  - change in modified TSS  
  - PsARC response  
  - HAQ score  
  - change in SF-36 health status  
  - change in sharp score components  
  - proportion of study participants with no change in modified TSS  
  - FACIT fatigue  
  - PASI 50/75/90 response  
  - change in DLQI.  
  QALYs were determined by the HAQ and PASI response. |

ACR, American College of Rheumatology; DLQI, dermatology life quality index; DMARD, disease-modifying anti-rheumatic drug; FACIT, functional assessment of chronic illness therapy; HAQ, health assessment questionnaire; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; QALY, quality-adjusted life year; SF, short-form questionnaire; SPC, summary of product characteristics; TNF-α, tumour necrosis factor-α; TSS, total sharp score.
1.2 **ERG comments on the MS**

1.2.1 **Population**

The evidence review group (ERG) highlighted that only a proportion of participants in the key studies of adalimumab had PsA that failed to respond to at least two DMARDs (42% in the M02-518 trial, and 56% in M02-570). Therefore, the adalimumab trial populations differed from that specified in the BSR guidelines for the use of anti-TNF-α therapy. However, independent expert opinion given to the ERG suggests that the participants in these trials ‘nevertheless represented a population with relatively severe PsA similar to those currently being treated in UK clinical practice’.

1.2.2 **Intervention**

The ERG did not comment on appropriateness, but the intervention matched the scope and was consistent with the marketing authorisation. The therapeutic indications within the summary of product characteristics (SPC) and the European Medicines Agency (EMEA) scientific discussions\(^1\) do not stipulate whether or not concurrent treatment can be given with adalimumab.

1.2.3 **Comparators**

The ERG interpreted that comparator interventions, including other anti-TNF-α agents such as etanercept and infliximab, could reasonably be considered conventional treatment strategies.

1.2.4 **Outcomes**

The ERG confirmed that the outcomes used, although limited for PsA, were appropriate.

1.3  Clinical specialists’ and patient experts’ statements

1.3.1 Summary of clinical specialists’ statements
Clinical specialists identified positive features of adalimumab, including safety and acceptability. The results of the adalimumab trials were considered to be generalisable to UK practice, but a lack of long-term evidence comparing adalimumab with existing anti-TNF-\(\alpha\) agents was noted. The view was expressed that adalimumab has similar efficacy to infliximab and is a useful alternative therapy. It was stated that the composition of the evidence base may be ‘problematic’, but there appears to be no reason why the current NICE guidance on anti-TNF-\(\alpha\) drugs would not apply to adalimumab. The clinical specialists highlighted the importance of considering improvements in both skin and joint outcomes. In addition, they noted that people with PsA may require multidisciplinary treatment involving both rheumatology and dermatology specialists.

1.3.2 Summary of patient experts’ statements
Patient/carer groups identified benefits of treatment with adalimumab, including reduced long-term disability and reliance on ‘powerful pain relief’, and improved mobility, quality of life, independence, active participation in the work place and ‘patient choice’. It was requested that the Committee gave particular consideration to the skin component and careful monitoring of people being treated with adalimumab. Self-injection and correct dosing, the possibility of unknown side effects and uncertain long-term efficacy were raised as concerns. One of the patient experts stated that ‘Patients tend to want to try anything, but become concerned about the long-term issues when they feel better’.

2  Clinical effectiveness evidence

2.1 Clinical effectiveness in the MS

2.1.1 Direct comparison
The manufacturer based its submission on four clinical trials.
Two double-blind, placebo-controlled randomised controlled trials (RCTs) of adalimumab (40 mg every other week) were presented. The trial participants comprised adults whose PsA had responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs; study M02-518/ADEPT, n = 313, 24-week duration) or DMARDs (study M02-570, n = 100, 12-week duration). Compared with placebo, adalimumab demonstrated a statistically significant improvement in:

- arthritic manifestations – American College of Rheumatology (ACR) response criteria/psoriatic arthritis response criteria (PsARC)
- joint destruction – mean change in modified total sharp score (TSS)
- skin manifestations – psoriasis area and severity index (PASI)/physician’s global assessment (PGA)
- disability – HAQ score

A prospective subgroup analysis of the M02-518 study indicated that response rates of those treated with adalimumab alone were similar to those for people treated with adalimumab and methotrexate.

No head-to-head comparisons of adalimumab with other licensed anti-TNF-α agents in the treatment of people with PsA were identified by the manufacturer.

The results of two open-label studies were also presented. One was an extension of the two RCTs mentioned previously (study M02-537, n = 395), in which all participants received adalimumab. In the second study (M04-724, STEREO, n = 253 in data presented), which was in progress when the MS was produced, adalimumab was added to ‘insufficient standard therapy’. The study population included people whose PsA did not respond to treatment with other anti-TNF-α agents.

Response rate (in % of participants at 24 weeks) appeared to be maintained (up to 88 weeks) in the M02-537 study.
The MS included a meta-analysis of two trials: M02-518 and M02-570. This was limited to arthritis outcomes and the 12-week time point because the M02-570 study did not report skin outcomes and continued as an open-label study after 12 weeks.

Similar rates of adverse events were observed in the adalimumab and placebo groups in the RCTs. Combined data indicated that 3% of people in the adalimumab-treated group and 4.3% of those in the placebo-treated group experienced a serious adverse event. Common treatment-related adverse events were upper respiratory tract infection, nasopharyngitis, injection site reactions, headache, aggravation of psoriasis and diarrhoea.

In response to a specific request to provide these data, the manufacturer indicated that anti-adalimumab antibodies were identified in [****] of people in the M02-537 open-label extension study who were receiving adalimumab. In those people who were not given concomitant methotrexate, the incidence was [*****] (******) compared with [*****] (******) when adalimumab was used as an add-on to methotrexate.

### 2.1.2 Indirect comparison

The manufacturer conducted an indirect comparison of adalimumab and other anti-TNF-α agents, applying its own methodology. The indirect analysis incorporated only one study for each anti-TNF-α agent because the inclusion criteria used by the manufacturer specified that: PASI, PsARC and ACR responses were reported for the study; study duration was at least 6 months; disease duration was more than 8 years; and DMARD therapy had been attempted at least once. The manufacturer did not use any 12-week response rates, and instead estimated the 12-week response rates from the 24-week response rates. Response data were adjusted across studies for the number of people with PsA with psoriasis at baseline for all drugs, but were based on the adalimumab data only. The indirect comparison relied on comparison of absolute response rates (after adjustment for the skin component) for the single arms of the different studies, without taking the placebo arms into consideration.

The manufacturer concluded that anti-TNF-α agents are broadly similar in terms of ACR response, but adalimumab and infliximab are superior to etanercept in terms of improvement of skin outcomes.
2.2 **ERG comments**

2.2.1 **Direct comparisons**

The ERG had some reservations about the generalisability of the adalimumab study populations to the UK PsA patient population, but accepted the evidence base. The ERG concurred that, based on the limited data available, adalimumab appeared to be effective in controlling PsA, including skin components of the disease, compared with placebo. Adverse events appeared to be similar between treatment and control groups and adalimumab was generally well tolerated. However, long-term safety data of adalimumab in the treatment of PsA is not yet available.

The ERG pointed out that there is uncertainty surrounding adalimumab and the possibility of it triggering the production of autoimmune antibodies. This could potentially result in discontinuation of therapy for a proportion of people receiving adalimumab.

2.2.2 **Indirect comparisons**

The ERG noted that the methods employed by the manufacturer were complex and lacked transparency, which made it difficult to assess the validity of the findings. The ERG expressed concern over the inclusion/exclusion criteria applied when studies were selected for the indirect comparison and about a number of assumptions and factors which, in the opinion of the ERG, may have resulted in bias and uncertainty in the results of the MS.

- The exclusion of all 12-week data from the studies, despite British Society for Rheumatology (BSR) guidelines recommending that continuation of treatment should be based on 12-week response, and the consequent recalculation of the 12-week response from the 24-week response in the modelling. The ERG requested clarification on this point from the manufacturer.
- The adjustment of the response data across studies according to the number of patients with skin involvement, based on data from the adalimumab study, and the application of this adjustment to the etanercept and infliximab studies. The ERG did not consider that the need for such
adjustment was adequately justified by the manufacturer’s data. However, the ERG analysed the effect of this adjustment (see page 78 of the ERG report) and concluded that it marginally improved the PsARC response estimates for adalimumab.

- The assumption of exchangeability of response rates after adjustment for the number of people with psoriasis at baseline; this meant that the absolute response rates (after adjustment for the skin component) for the single arms of the different studies were directly compared with each other.
- The approaches used to estimate correlation between response parameters.
- The influence of including 24-week data from M02-570 on the adalimumab response in the synthesis, and also the potential influence on etanercept and infliximab responses in the Bayesian synthesis. The ERG requested clarification on this point from the manufacturer.

2.2.2.1 The ERG requested more information and analyses from the manufacturer, particularly regarding the evidence synthesis used for the indirect comparison. This is described in section 3.3.

3 Cost-effectiveness evidence

3.1 Cost effectiveness in the MS

The manufacturer submitted a de novo cost–utility model assessing the impact of treatment with adalimumab on a composite of joint and skin outcomes. It compared this with ‘conventional’ (non-biological) DMARDs (when used according to the BSR treatment guidelines). The model used a Monte-Carlo simulation at the patient level. In the model, treatment only continued with a PsARC response at 12 weeks. Based on the ACR and PASI response, regression analysis was used to predict the HAQ and PASI scores of the individual modelled patients. The predicted HAQ and PASI scores were then used to estimate both costs and utilities. Cycle length was 6 months, and a lifetime time horizon (as well as alternatives) was presented.
The annual acquisition cost of adalimumab to the NHS is £9295 per patient (based on 26 injections per year). The annual acquisition costs of etanercept are £9295 and for infliximab £13847 and £10386 (first and subsequent year of treatment, respectively). The cost of adverse events was not included in the modelling.

The results for the base-case model from the manufacturer for a lifetime horizon were as follows.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean cost (£)</th>
<th>Mean QALYs</th>
<th>ICER (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>61,308</td>
<td>8.18</td>
<td>25,991</td>
</tr>
<tr>
<td>Etanercept</td>
<td>65,627</td>
<td>8.15</td>
<td>Dominated</td>
</tr>
<tr>
<td>Infliximab</td>
<td>81,614</td>
<td>8.27</td>
<td>209,572</td>
</tr>
<tr>
<td>DMARD</td>
<td>28,518</td>
<td>6.91</td>
<td>-</td>
</tr>
</tbody>
</table>

DMARD, disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The ICER for adalimumab compared with DMARD was particularly sensitive to the following alternative assumptions.

- Use of the Toronto HAQ progression for natural history: ICER £47,404.
- Use of SF-6D as a basis for utility regression: ICER £62,360.

The ERG requested more information and analyses from the manufacturer. This is described in section 3.3.

### 3.2 ERG comments

The ERG acknowledged that there were limited data available to carry out a cost-effectiveness analysis for adalimumab in PsA and that the attempt to incorporate the differential impact of alternative therapies on the psoriasis and arthritis components of PsA was a particular strength of the modelling. The ERG also considered it not unreasonable to exclude the cost of adverse events from the modelling.

However, the ERG identified a number of issues that appeared to compromise the validity of the model results, including:
• the failure to consider all relevant evidence (for example exclusion of 12-week trial data) in estimating response rates, and the adjustment used by the manufacturer to estimate 12-week response parameters from 24-week trial results; this was particularly important because 12-week responses were central to the model, in that they determined initial treatment response and consequently the decision about whether to continue treatment or switch (see section 3.3)
• the exclusion of a potentially relevant comparator (palliative care; see section 3.3)
• the assumption of exchangeability of absolute response rates (after adjusting for differences between the proportion of study participants with skin involvement)
• the utility data feeding into the model were derived from a regression analysis using the EuroQol (EQ)-5D data from M02-518, supplemented with another study with a population that appears to experience more severe PsA. The SF-6D data collected in M02-518 indicated better utilities, with a resulting ICER of £62,360.
• The annual HAQ progression rate of 0.07 used in the control arm of the manufacturer’s model was derived from people with severe PsA who were receiving palliative care (that is, not DMARDs). This HAQ progression rate is 2.5 times higher than a recently published HAQ progression rate of 0.028 in people whose PsA is responding to treatment with DMARDs (leflunomide or ciclosporine). When an alternative assumption was used by the manufacturer (mean annual HAQ progression 0.0085) the resulting ICER was £47,404.

3.3 Additional analysis

The ERG requested clarification and considerable re-analysis and re-modelling on the following points.

3.3.1 Exclusion of 12-week data and extrapolation of 12-week response data from 24-week data

The ERG requested that all available evidence from 12-week and 24-week studies be included in the evidence synthesis underpinning the indirect comparison. The National Institute for Health and Clinical Excellence
manufacturer provided this information based on six studies (pages 99–100 of the ERG report). The 12-week response data for etanercept and infliximab were higher than the 24-week results, and therefore the previous adjustment made by the manufacturer underestimated the 12-week response rate for the comparators. In addition, the 12-week data for adalimumab, which were excluded from the initial analysis, were lower than those reported at 24 weeks. Therefore, the original adjustment made by the manufacturer appears to be in favour of adalimumab.

The new evidence synthesis was used to calculate new response rates for the model. The ERG noted that a constraint was used by the manufacturer on the 12-week response rates, in that they could not exceed the 24-week response rates, which disadvantages etanercept and infliximab in the analysis.

The results of the modelling incorporating 12-week data for a lifetime horizon were as follows.

<table>
<thead>
<tr>
<th></th>
<th>Total cost (£)</th>
<th>Total QALYs</th>
<th>ICER (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>69,677</td>
<td>8.14</td>
<td>31,458</td>
</tr>
<tr>
<td>Etanercept</td>
<td>72,729</td>
<td>8.29</td>
<td>19,856*</td>
</tr>
<tr>
<td>Infliximab</td>
<td>87,675</td>
<td>8.41</td>
<td>114,234</td>
</tr>
<tr>
<td>DMARD</td>
<td>28,518</td>
<td>6.83</td>
<td>-</td>
</tr>
</tbody>
</table>

* etanercept extendedly dominates adalimumab.

DMARD, disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

This analysis, however, still incorporated open-label (non-controlled) results from one study (M02-570). The absolute event rates from the M02-570 study were markedly higher than in the controlled M02-518 study.
### 3.3.2 Exclusion of the open-label portion of the M02-570 study from the evidence synthesis

The ERG requested a re-run of the evidence synthesis and model excluding the 24-week response data (open-label portion) from the M02-570 study. The results for a lifetime horizon were as follows.

<table>
<thead>
<tr>
<th></th>
<th>Total cost (£)</th>
<th>Total QALYs</th>
<th>ICER (£)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>67,457</td>
<td>8.35</td>
<td>25,893</td>
<td>vs DMARD</td>
</tr>
<tr>
<td>Etanercept</td>
<td>67,670</td>
<td>8.20</td>
<td>Dominated</td>
<td>by adalimumab</td>
</tr>
<tr>
<td>Infliximab</td>
<td>84,542</td>
<td>8.51</td>
<td>122,532</td>
<td>vs adalimumab</td>
</tr>
<tr>
<td>DMARD</td>
<td>28,271</td>
<td>6.83</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

DMARD, disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The PsARC response from the M02-570 (open-label) study at 24 weeks (74% for adalimumab) was higher than the corresponding 24-week estimate (60%) from the M02-518 study. The exclusion of the M02-570 24-week results resulted in an expected reduction in the PsARC response rate from the revised evidence synthesis for adalimumab. The ERG expected that exclusion of this study would result in less favourable cost-effectiveness estimates for adalimumab. However, this was not the case, which raised concern about face validity of the analysis.

Furthermore, the PsARC response rates for both infliximab and etanercept also appear to have been significantly reduced in the re-run analysis from 67% to 60% for etanercept and from 62% to 58% for infliximab. The ERG was unsure why the exclusion of the 24-week results from M02-570 would alter the PsARC response in this manner, and therefore concluded that the revised synthesis does not appear to be sufficiently robust and that the subsequent cost-effectiveness estimates may not be valid.

### 3.3.3 Analysis of subgroups with and without skin involvement

The ERG requested an analysis that determined the relative cost effectiveness of adalimumab in groups of people with PsA with skin disease and those with PsA but...
no skin disease (that is, equal to or less than 3% body surface area [BSA]). The results were as follows.

<table>
<thead>
<tr>
<th></th>
<th>Total cost (£)</th>
<th>Total QALYs</th>
<th>ICER (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With skin involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>59,487</td>
<td>7.83</td>
<td>23,039</td>
</tr>
<tr>
<td>Etanercept</td>
<td>66,881</td>
<td>7.88</td>
<td>Dominated by adalimumab</td>
</tr>
<tr>
<td>Infliximab</td>
<td>82,625</td>
<td>8.04</td>
<td>107,177</td>
</tr>
<tr>
<td>DMARD</td>
<td>32,381</td>
<td>6.65</td>
<td>-</td>
</tr>
<tr>
<td><strong>Without skin involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>56,204</td>
<td>8.58</td>
<td>32,461</td>
</tr>
<tr>
<td>Etanercept</td>
<td>60,516</td>
<td>8.69</td>
<td>39,646</td>
</tr>
<tr>
<td>Infliximab</td>
<td>73,487</td>
<td>8.58</td>
<td>Dominated by adalimumab</td>
</tr>
<tr>
<td>DMARD</td>
<td>20,317</td>
<td>7.48</td>
<td>-</td>
</tr>
</tbody>
</table>

DMARD, disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

It should be noted that these results are based on the initial analysis, where the 12 week data were extrapolated from the 24 week data and include the open-label, 24-week response data from the M02-570 study. The results indicate that adalimumab is more cost effective in people with skin involvement than in people without skin involvement.

### 3.3.4 DMARD use at baseline

The ERG requested an analysis based on DMARD use at baseline (using groups of people who had tried fewer than two DMARDs, or two or more DMARDs) but this was not provided by the manufacturer. The manufacturer argued that variation in the number of DMARDs used at baseline was small and that this was therefore not a significant predictor of HAQ or PASI in the model. The ERG accepted the latter point, but felt that the differences in the response parameters themselves (ACR and PASI) might be partially explained by the number of previous DMARDs used.
3.3.5  Exclusion of DMARD drug cost

The ERG requested a sensitivity analysis to explore the effects of excluding DMARD costs (in the base case only 100% continuation on DMARDs in the control arm was modelled). The ERG noted that the BSR guidelines indicate that after inadequate response to DMARDs, a proportion of people move into palliative care. The ERG also suggested that the analysis had included costs for DMARD use, but had not considered the treatment efficacy of this regimen, thereby underestimating its cost effectiveness and increasing the relative cost effectiveness of the anti-TNF-α agents. These analyses were not provided by the manufacturer, who asserted that DMARD therapy (for 100% of patients) was the appropriate comparator and that these costs would not have a major impact on the cost effectiveness of adalimumab with respect to other anti-TNF-α agents. The ERG was therefore unable to judge the robustness of the base-case analysis or the effect of excluding DMARD costs.

3.3.6  More conservative scenario for HAQ rebound effect

The manufacturer’s model included the rebound equal to gain (on stopping anti-TNF-α therapy) assumption. The ERG requested a sensitivity analysis to explore the effect of a more conservative assumption of the rebound effect (‘rebound to natural history’). The manufacturer did not provide the requested analysis, stating that the assumptions were not ‘unduly optimistic’. The manufacturer also indicated that their model was not sufficiently flexible to explore this issue.

The manufacturer recognised that a more conservative rebound assumption might reduce benefits calculated in their model. Making reference to NICE technology appraisal 104 (etanercept and infliximab for the treatment of adults with psoriatic arthritis), the ERG reported that the ICER for etanercept in the York model increased by approximately 40% (rebound back to natural history: £27,681; rebound equal to gain: £16,801 – corrected from ERG report). The ERG emphasised that these data are presented only as a ‘point of reference’, and that, in the absence of additional analysis from the manufacturer, it was not possible to determine the actual impact of varying HAQ rebound assumptions on the cost effectiveness of adalimumab.
3.3.7 ERG conclusions on the cost effectiveness of adalimumab

Although the manufacturer attempted to address a number of issues during additional work, the subsequent results were not considered sufficient to resolve the issues raised for clarification by the ERG. After reviewing the requested re-analysis, the ERG felt that the results lacked face validity, bringing into question the robustness of the evidence synthesis approach and/or assumptions used by the manufacturer.

The ERG concluded that the revised synthesis provided by the manufacturer does not appear to be sufficiently robust and that the subsequent cost-effectiveness estimates may not be valid.

4 Authors

Dr Ruairidh Hill and Dr Elisabeth George, on behalf of the Committee Chair (Professor Andrew Stevens) and the Lead Team (Professor David Chadwick, Dr Rachel Elliot).