Assessment Group Report

Exploratory analyses following comments received in April 2015 and further clarification on Assessment Group model parameter values.

Produced by ScHARR, University of Sheffield

Authors Matt Stevenson, Professor of Health Technology Assessment, ScHARR

Allan Wailoo, Professor of Health Economics, ScHARR

May 2015

Source of funding: This work was commissioned by the NIHR HTA Programme as project number 11/74.

Background

On the 17th of March 2015 four documents were put on the NICE website.

These were:

- An updated version of the Assessment Group report having taken into consideration comments received on the previous report and executable model. [1]
- A brief summary of the aforementioned Assessment Group report. [2]
- A NICE decision support unit (DSU) report investigating the progression of disease on people with rheumatoid arthritis treated with non-biologic therapies. [3]
- A report indicating the impact on the incremental cost-effectiveness ratios (ICERs) that would be implied by the information provided in the NICE DSU report. [4]

A separate document provided revised ICERs following the identification and correction of errors.[5] The purpose of this document is to conduct further cost-effectiveness modelling where it is believed that doing so would be of value to the Appraisal Committee. Given the large number of analyses presented in the updated version of the Assessment Group report[2] not all scenarios have been re-analysed, only those that were most pertinent with the assumption that changes in the ICERs could be extrapolated for the remaining results.

The additional analyses have been subdivided into the following categories:

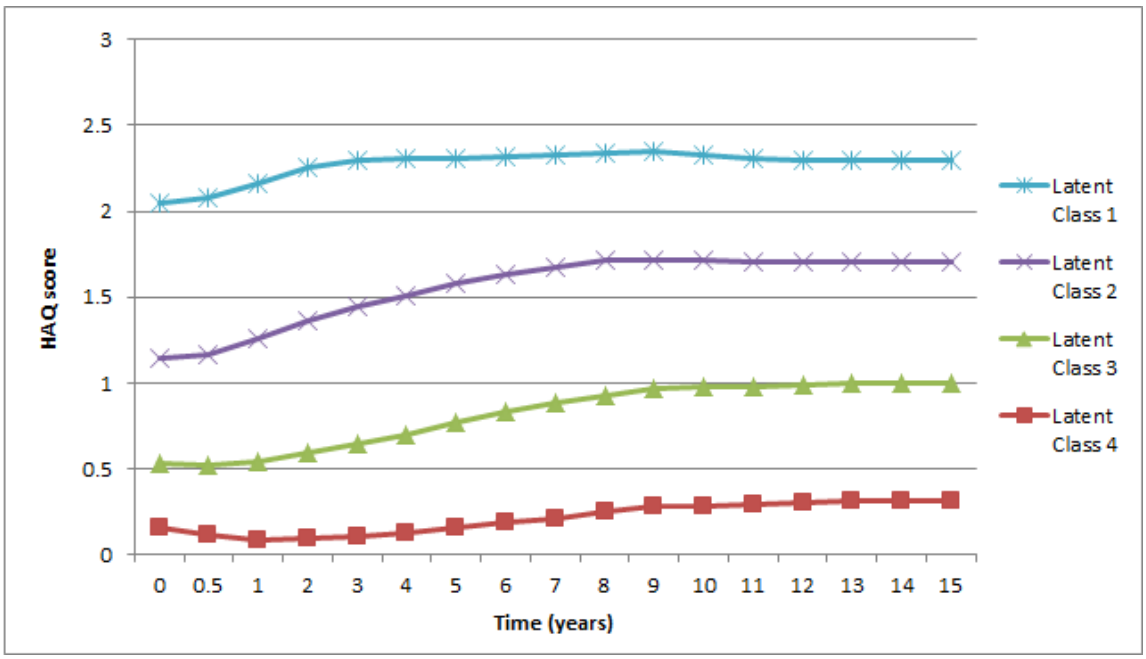
1) Exploratory scenarios that were mentioned within the comments received
    - Assuming that latent classes 3 and 4 would continue to experience a worsening in HAQ progression beyond 15 years
    - A reduction of the monitoring costs to one-third of that assumed in the base case
    - The removal of rituximab and tocilizumab from a bDMARD treatment sequence
    - Reducing the assumed percentage (10%) of patients who would require district nurse help with subcutaneous injections
2) Incorporation of biosimilars for infliximab
3) Further clarification of Assessment Group parameter inputs
    a. On the relationship between HAQ and pain
    b. On the assumed relationship between EULAR and ACR values

Exploratory analyses

Increasing the duration of estimated HAQ progression

Comments were received that stated that changes in HAQ were observable at 15 years for latent classes 3 and 4, whereas the Assessment Group assumed that it would be flat for all classes. The HAQ progression in the base case is shown in Figure 1.

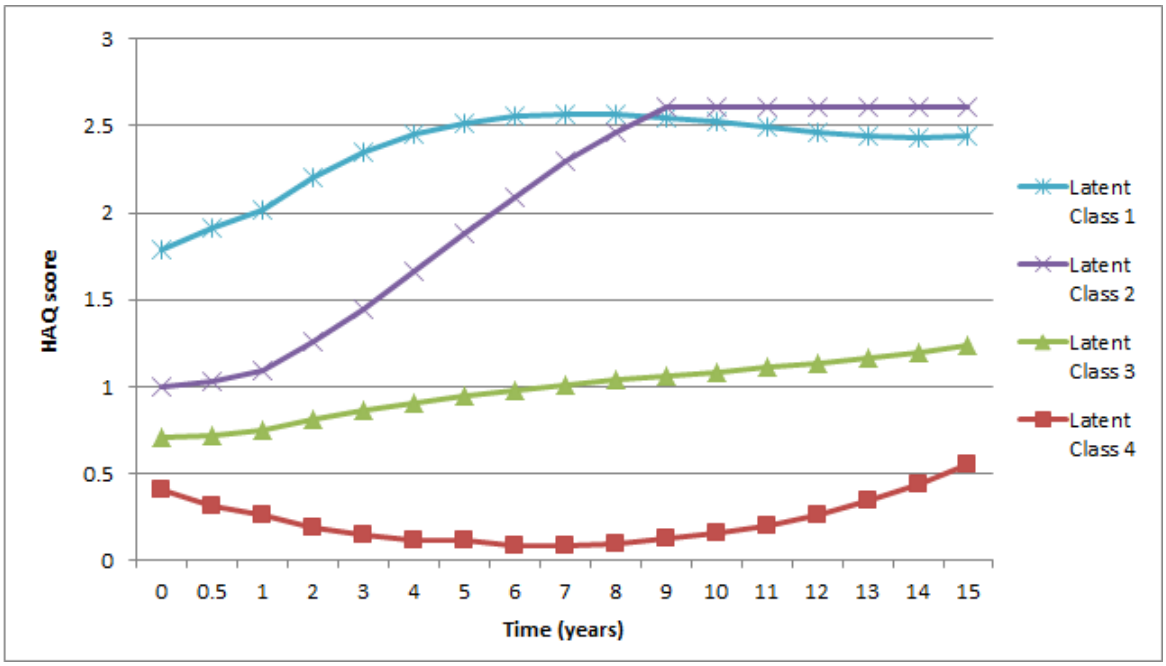
Figure 1: The assumed HAQ progression by latent class in the base case



The Assessment Group had stated that any assumption of continuing HAQ progression in latent classes 3 and 4 would have little impact on the results. The rationale for this was: the small numbers of patients in latent classes 3 and 4 (particularly in the severe RA group); the effects of discounting; the typical life expectancy of patients simulated in the decision problem; and that the curves appear flat

Nevertheless, analyses were run assuming that the progressions between years 12 and 15 within latent classes 3 and 4 were maintained until year 40. Analyses were run for the base case population, and also for the exploratory analyses undertaken where those patients with the greatest HAQ progression could be determined.[4] For reference, the assumed HAQ progressions for these patients are provided in Figure 2. Analyses were undertaken for those with severe and those with moderate RA.

Figure 2: The assumed HAQ progression by latent class in those patients with the greatest HAQ progression (Exploratory analyses)



Results are provided in terms of median ICERs (

Table **1**) followed by the fully incremental ICERs. (

Table **2** to Table 5). It is seen that the reduction in the median ICER is relatively small.

Table 1: Summary of median ICERs when assuming that there is ongoing HAQ progression between years 15 and 40 for latent classes 3 and 4

	All patients		Those patients with greatest HAQ progression	
	ERG base case	Assuming HAQ progression in latent classes 3 and 4	ERG base case	Assuming HAQ progression in latent classes 3 and 4
Severe RA	£41,600	£40,800	£25,300	£23,900
	All patients		Those patients with greatest HAQ progression	
	ERG base case	Assuming HAQ progression in latent classes 3 and 4	ERG base case	Assuming HAQ progression in latent classes 3 and 4
Moderate RA	£51,100	£49,100	£28,500	£25,700

All numbers rounded to the nearest £100

Table 2: Results assuming HAQ progression in latent classes 3 and 4 between years 15 and 40 – severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 40,808	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 38,071	£ 38,071
IFX + MTX	[redacted]	[redacted]	£ 38,678	Dominated
CTZ + MTX	[redacted]	[redacted]	£ 40,057	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 41,070	Dominated
GOL + MTX	[redacted]	[redacted]	£ 40,979	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 41,027	£ 74,212

ABT i.v. – abatacept intravenous; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 3: Results assuming HAQ progression in latent classes 3 and 4 between years 15 and 40 and that those with greatest HAQ progression could be identified – severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 24,379	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 22,044	£ 22,044
IFX + MTX	[redacted]	[redacted]	£ 22,296	Dominated
ADA + MTX	[redacted]	[redacted]	£ 23,941	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 23,433	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 23,940	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 24,420	£ 60,288

ABT i.v. – abatacept intravenous; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 4: Results assuming HAQ progression in latent classes 3 and 4 between years 15 and 40 – moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 51,180	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 46,882	£ 46,882
IFX + MTX	[redacted]	[redacted]	£ 47,919	Dominated
ADA + MTX	[redacted]	[redacted]	£ 49,191	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 48,600	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 49,133	Dominated
ETN + MTX	[redacted]	[redacted]	£ 49,602	£ 67,942

ABT i.v. – abatacept intravenous; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Table 5: Results assuming HAQ progression in latent classes 3 and 4 between years 15 and 40 and that those with greatest HAQ progression could be identified – moderate, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 26,619	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 23,498	£ 23,498
IFX + MTX	[redacted]	[redacted]	£ 24,274	Dominated
ADA + MTX	[redacted]	[redacted]	£ 25,687	Dominated
CTZ + MTX	[redacted]	[redacted]	£ 25,231	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 26,020	Dominated
ETN + MTX	[redacted]	[redacted]	£ 26,431	£ 80,858

ABT i.v. – abatacept intravenous; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Reducing the costs of monitoring.

The costs of monitoring for patients receiving bDMARDs was estimated to cost £134 per month, primarily composed of one hospital outpatient appointment. It was suggested that a more appropriate monitoring schedule would be a hospital outpatient appointment every three months rather than monthly. Clinical advice was sought, which suggested, on average, that a less frequent monitoring schedule would be more realistic. However, the clinical advice did not support a differential frequency of hospital outpatient visits, on average, for those on bDMARDs and cDMARDs. As the costs would be assumed to be the same between bDMARDs and cDMARDs, although the absolute costs for both strategies would be lower there would be no change in the incremental costs between strategies and no further analyses were run.

Removing rituximab and tocilizumab from the sequence

Comment was made that the follow-on costs of rituximab and tocilizumab were adversely affecting the possibility of the original bDMARD being cost-effective, although it is presumed that the patient access scheme relating to tocilizumab was not used in the exploratory analysis conducted by Pfizer when initial bDMARD costs were set to zero. To test this hypothesis, a scenario analysis was undertaken in which only one bDMARD was allowed before progressing to non-biologic therapy. The fully incremental results from this analysis are shown in Table 6. The median ICER increases to £46,100. It is believed that this is due primarily to rituximab being cheaper than other bDMARDs but having a similar efficacy.

Table 6: Results when allowing only one bDMARD in a sequence – severe, MTX-experienced, RA population

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
ABT i.v. + MTX	[redacted]	[redacted]	£ 41,252	£ 41,252
IFX + MTX	[redacted]	[redacted]	£ 42,611	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 49,827	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 46,073	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 47,322	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 46,123	Ext Dominated
TCZ + MTX	[redacted]	[redacted]	£ 46,557	£ 57,220

ABT i.v. – abatacept intravenous; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

Reducing the percentage of patients who require district nurse help in administering subcutaneous injections.

In the original submission it was assumed that 10% of people requiring subcutaneous injections would need assistance from a district nurse. Comments from The British Society of Rheumatology suggest this figure is too high and would unfairly add to the cost of bDMARDs. No additional runs were taken on this parameter for the following reasons:

- The percentage cost of district nurse time is very small compared with the total cost. For example etanercept is assumed to cost £924.49 per month which significantly outweighs the £3.05 district nurse cost assumed per injection
- A 10% reduction in the cost of infliximab to consider the introduction of biosimilars (see later) did not show a large change in the ICER (see next section). As in the etanercept example district nurse cost is 0.3% of the acquisition cost we do not believe this will have a marked impact
- The value used in the Assessment Group report were similar to those used in the company submissions
- It is unclear what are the true proportions requiring district nurse assistance for those on bDMARD and those on cDMARDs.

Incorporation of infliximab biosimilars

Two biosimilars for infliximab have been released: remsima (Napp Pharmaceuticals) and inflectra (Hospira UK). These both have the same list price of £377.66 per 100mg vial, compared with a branded infliximab (remicade) price of £419.62, which represents a reduction of 10%.

This single change would be unlikely to affect the median ICER, as the ICER for infliximab was typically below the median and a price reduction would lower the ICER. As such, only the fully incremental analyses have been provided (Table 7)

Table 7: Results when setting the price of infliximab to that of a biosimilar

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
IFXb + MTX	[redacted]	[redacted]	£ 37,185	£ 37,185
TCZ + MTX	[redacted]	[redacted]	£ 41,240	Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 38,607	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 41,426	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 40,480	Dominated
GOL + MTX	[redacted]	[redacted]	£ 41,562	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 41,414	£ 85,751

ABT i.v. – abatacept intravenous; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; GOL – golimumab; IFXb – infliximab biosimilar; MTX – methotrexate; TCZ – tocilizumab
CPQ – cost per QALY gained. Ext - extendedly

The change in the ICER for biosimilar infliximab is less than £3,000 per QALY gained. Whilst there is a 10% discount on the acquisition costs of infliximab, costs of monitoring and subsequent therapies (rituximab, tocilizumab and where appropriate non-biologic therapies) have not been reduced.

One comment to NICE asked that the price of infliximab biosimilars to be set lower than the list price to reflect the 'actual acquisition price' but this was not allowed given the remit of the Assessment Group.

Further clarification of Assessment Group parameter inputs

Request for further clarification regarding the relationship between HAQ and pain.

The Assessment Group model is HAQ based. In order to transform the HAQ at any point in time for the individual patients in the model, into a utility score (and hence QALYs), the model makes use of a mapping function. This estimates EQ-5D utility as a function of HAQ and other variables like age and pain. The model therefore needs to estimate the patient's level of pain.

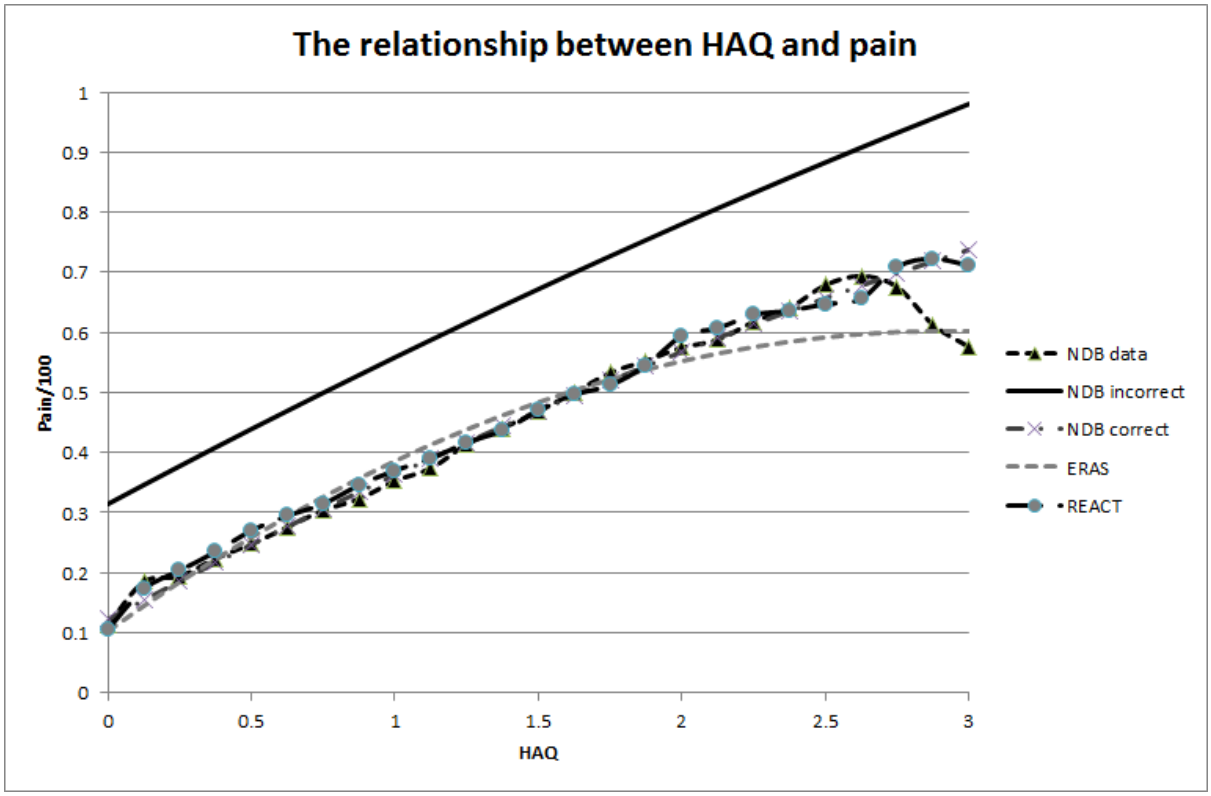
In the original Assessment Group report, two data sources were identified for this: the NDB and ERAS. The NDB was used but a plot was provided that showed how the data sources were very similar so this was not envisaged to be a contentious issue.

However, in the consultation exercise two consultees (Abbvie and Pfizer) commented on this aspect of the model. Abbvie argues that a) the values we had reported to estimate pain from HAQ were a poor fit to the plot of the NDB data and b) data from their REACT clinical trial gave a very different relationship.

We investigated these claims and identified an error leading to an underestimation in estimated pain from HAQ. This was corrected and the new function now correlates very closely to the NDB data. We previously reported how this is very similar in the ERAS dataset. We also find this is very close to the data provided by Abbvie from REACT.

Figure 3 demonstrates the data from the NDB and the functions used to estimate that data in the previous Assessment Group model (which overestimated the relationship), the new estimate, and contrasts this with ERAS and the REACT data (all observations) supplied by Abbvie.

Figure 3: Relationship between HAQ and pain estimated by the NDB, ERAS and the REACT trial



We agree with Pfizer and Abbvie that there was an error in the original implementation of the model. There is now three-way validation of the estimates used in the AG model (ERAS, NDB and REACT). The AG base case model uses the NDB derived estimates. This correction was shown to increase the ICER by approximately £18,000 (see Figure 4 and accompanying text in the summarised Assessment Group document).[2] An additional analysis to assess the comparability between the ICERs predicted by ERAS and the corrected NDB mappings showed that the ICERs for the entire severe population using the ERAS mapping was in the region of £10,000 more than when using the NDB mapping.[5] This increase was primarily caused by lower predicted rates of pain at HAQ scores of 2 and above in the ERAS mapping (Figure 3).

The assumed relationship between ACR and EULAR values

On submission of the original Assessment Group report it was unclear whether the data provided by the Veterans Affairs Rheumatoid Arthritis (VARA) registry were academic in confidence. VARA is a multi-centre, US database of veterans over the age of 19 years. Subsequently it was ascertained that this was not the case and the relationship has been shown in the updated Assessment Group report.[1]

For ease of reference the table (Table 164 in the updated Assessment Group report[1]) has been reproduced in Table 8.

Table 8: The relationship between EULAR responses and ACR responses in the VARA databases

	Less	***ACR20***	***ACR50***	***ACR70***	***total***
EULAR ESR, all patients					
EULAR None	755	4	2	0	759
Mod	136	27	2	2	163
Good	57	26	10	2	83
EULAR ESR, severe active					
EULAR None	72	2	0	0	74
Mod	33	19	0	0	52
Good	3	9	5	1	12

These results were not propagated through the model probabilistically, but the Assessment Group has no reason to believe that having done this would significantly affect the mean ICER, although do comment that if the data were continuity corrected to allow a non-zero probability of transition, for example between ACR 50 and a moderate EULAR response, the produced results may be slightly unfavourable to bDMARDs. The median ICERs originally produced using EULAR data alone, and those from an ACR response mapped to EULAR (Table 171 in the updated Assessment Group report[1]) are similar which reassures the Assessment Group that any mapping has not caused significant bias.

Conclusion

None of the exploratory analyses undertaken significantly affected the ICER which typically remained greater than £40,000 per QALY gained for the entire severe RA populations and greater than £50,000 per QALY gained for the entire moderate population. The reduction of the price of infliximab biosimilars compared with infliximab resulted in an estimated ICER of £37,200 within the severe RA population for the strategy using biosimilar infliximab first-line in severe RA patients.

[1] Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J et al. 2015 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only: systematic review and economic evaluation https://www.nice.org.uk/guidance/gid-tag313/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-appendix-1-updated-assessment-report2

[2] Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J et al. 2015 Addendum to: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only: systematic review and economic evaluation. Amendments to the model inputs since the first NICE appraisal committee and how these changes impact on the estimated cost per QALY gained ratios. https://www.nice.org.uk/guidance/gid-tag313/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-assessment-report-addendum2

[3] Gibson L. Hernandez Alava M, Wailoo A. 2015 Progression of disease on people with rheumatoid arthritis treated with non biologic therapies. https://www.nice.org.uk/guidance/gid-tag313/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-decision-support-unit-report

[4] Stevenson M, Wailoo A. 2015 Assessing how the results from the DSU report on HAQ progression affect the cost per QALY gained ratios https://www.nice.org.uk/guidance/gid-tag313/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-appendix-1-updated-assessment-report2

[5] Stevenson M, Wailoo A. (2015) Estimated cost per QALY ratios for bDMARD strategies following the correction of identified errors.