Assessment Group Report

Assessing how the results from the DSU report on HAQ progression affect the cost per QALY gained ratios

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1. Introduction

This report is a follow-up report to the initial report presented to the NICE Appraisal Committee in August 2013 which can be found on the NICE website. (https://www.nice.org.uk/guidance/gid-tag313/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-assessment-report2). For clarity the report on the NICE website will be called 'August2013 report'.

Following consultation on the August 2013 report and the accompanying mathematical model (denoted as 'August 2013 model') legitimate errors and omissions were identified which have been addressed in an accompanying report [1]: this report will be denoted the 'February 2015 report' for clarity. All analyses presented in this report have been undertaken using the updated model detailed in the February 2015 report.

Due to the sensitivity of the cost per quality adjusted life year (QALY) gained for biologic disease-modifying anti-rheumatic drugs (bDMARDs) to the estimated Health Assessment Questionnaire (HAQ) progression whilst on conventional disease-modifying anti-rheumatic drugs (cDMARDs), NICE commissioned the Decision Support Unit (DSU) to undertake a review of the literature and analyses of any databases that could be identified and accessed. The conclusions from this report are presented elsewhere,[2] and for clarity this report is henceforth denoted 'the DSU report'. The aim of this report is to assess the sensitivity of the cost per QALY gained for bDMARDs to scenarios suggested by the DSU report that were deemed worthy of investigation.

In addition, due to comments raised during the discussions around the DSU scope, a set of analyses has been undertaken focussing on patients whose diagnosis of RA was from 2010 or later as it was hypothesised that such patients may have more scope for improvement with bDMARD treatment than patients with a long duration of disease, who may already have significant non-reversible joint damage. For clarity these patients are denoted 'post 2009 population'.

For brevity, full definitions of components of the decision problem have not been provided in this report. Further details can be found within the February 2015 report.

The incremental cost effectiveness ratios (ICERs) in terms of cost per QALY for bDMARDs in three populations were explored in the February 2015 report. These populations were: those with severe active RA (defined by a disease activity score of 28 joints (DAS28) score of $\geq$5.1) who were cDMARD naïve (Population 1 in the NICE scope); those with severe RA who were cDMARD

experienced which formed Population 2 in the NICE scope; and Population 3 in the NICE scope, those with moderate-to-severe active RA (defined as a DAS28 score between 3.2 and 5.1).

All analyses have been undertaken within the Assessment Group's model. A potential ambiguity within the DSU specification document has been highlighted regarding the phrase 'Any results of analyses using the estimates in the manufacturers' models.' The Assessment Group believe that this denoted incorporating the values preferred by the companies within the Assessment Group model, which has been undertaken. The Assessment Group does not believe this related to incorporating new HAQ progressions within each of the companies' models, which has not been undertaken.

2. Changes to the assumed HAQ progression following the DSU Report.

A comprehensive analysis on the most likely HAQ progression for patients with RA has been presented in the DSU report. The findingsof the DSU report does not support the Assessment Group altering its base case scenario, and as such the results presented in the February 2015 report remain the Assessment Group's best estimation of the likely ICERs of bDMARDs.

However, exploratory analyses have been conducted to assess the impact of the ICER were it possible to identify (without cost) the patients within each of the four previously defined latent classes in whom HAQ increases most in the 15 years since initiation of cDMARDs.See section 4.5.4 of the DSU report for further information. For clarity these patients will henceforth be called 'patients with the greatest HAQ progression'. It is not possible currently to identify such patients and thus these results are provided purely to illustrate a plausible lower bound on the ICER should techniques to identify such patients. For further details on the derivation of the four latent classes see the February 2015 report and the DSU report.

The trajectories for patients with the greatest HAQ progression rates using the Roy-Muthen method are shown in Figure 25 of the DSU report and using the DSU report nomenclature are the latent dropout classes denoted C1 for latent classes 1 and 2, latent dropout class C3 for latent class 3 and latent dropout class C2 for latent class 4. For use as inputs into the mathematical cost-effectiveness model, it was assumed that the drop in HAQ predicted at approximately 12 years for patients in latent class 2 was subject to substantial uncertainty and that it appeared reasonable to assume that HAQ would be flat from 9 years to 15 years at the average HAQ value between years 9 and 15. The HAQ progression used in the model for patients with the greatest HAQ progression in each of the four latent classes is shown in Figure 1. For all latent classes it was assumed that HAQ would be flat beyond 15 years. This assumption is supported by the data for latent Classes 1 and 2, where the majority of patients reside, there is no indication of a trend for increasing HAQ between 10 and 15 years.

It is stressed that the HAQ changes are utilised in the model as relative changes and are not assumed to be absolute HAQ scores. An example is provided to illustrate this further: a patient who is sampled to have an initial HAQ score of 1.5 would have the same projected progression as a patient identical in all other respects bar initial HAQ score. If this second patient was simulated to have a HAQ score of 1.25, then there would be, on average, a difference in HAQ of 0.25 between the patients throughout the model.

For comparison the HAQ progression assumed in the base case is provided in Figure 2: it can be seen that the rate of progression in latent Classes 1 and 2, where the majority of patients reside, is much greater in the exploratory analyses

Figure 1: The assumed HAQ progression by latent class in those patients with the greatest HAQ progression (Exploratory analyses)

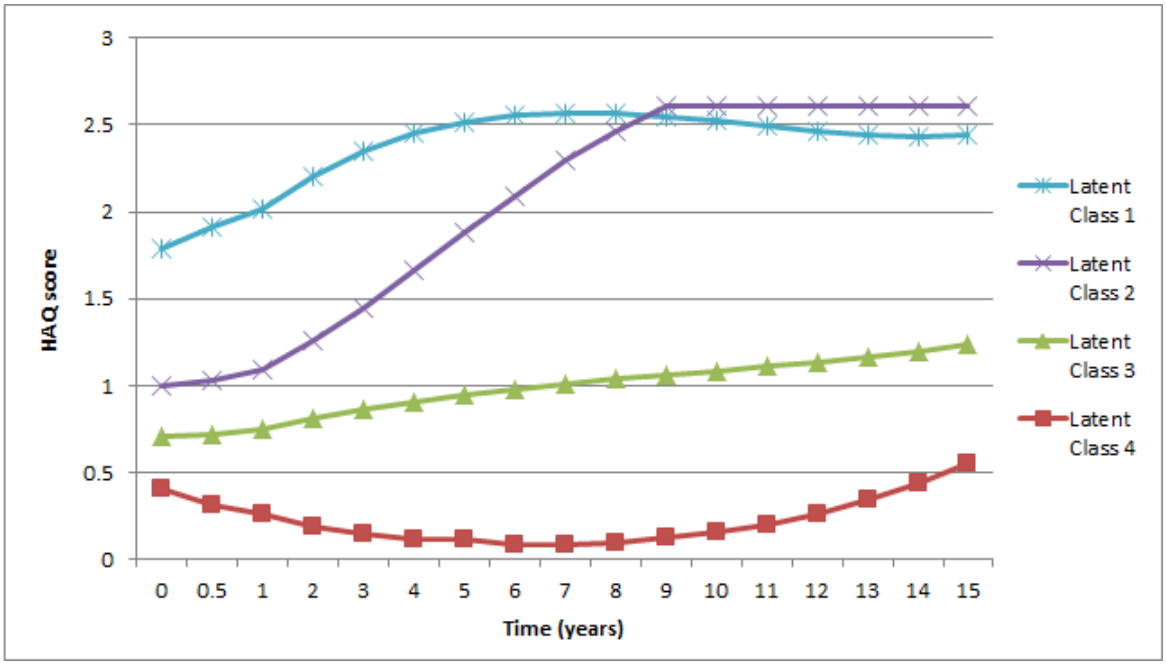
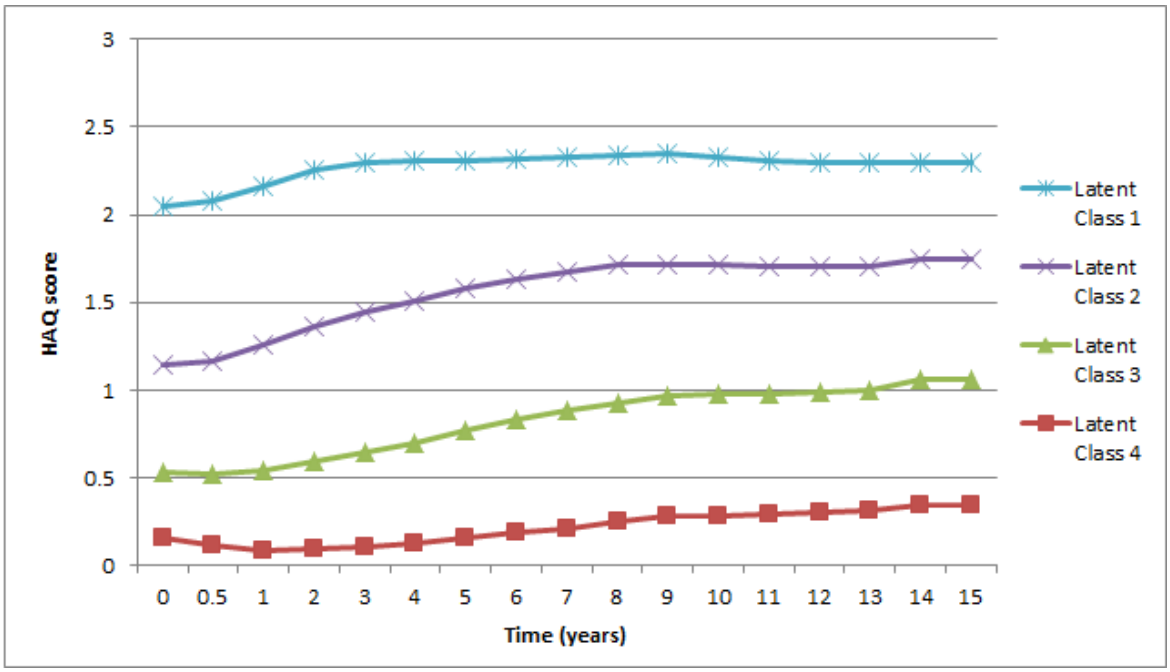


Figure 2: The assumed HAQ progression by latent class in the base case



In the analysis within the February 2015 report the mean characteristics of the full, UK treated biologics population from the BSRBR estimates that the vast majority of patients (approximately 99%) would be allocated to be in latent classes 1 and 2 (see Table 30 of the DSU report). The assumed patient characteristics for this population are provided in Table 2 of the DSU report.

When analysing the post 2009 population the numbers in each latent class change, which may reflect differences in early treatment patterns for the more recently diagnosed. For the severe RA group the probability of patients with the mean characteristics being allocated to latent classes 1 and 2 was 96%, this proportion was 82% for those in the moderate-to-severe RA group (see Table 30 of the DSU report). The assumed patient characteristics for the post 2009 population are provided in Table 2 of the DSU report.

3. **Assessing the impact of using a patient population with a lesser disease duration**

The Assessment Group was provided with data from the British Society for Rheumatology Biologics Register (BSRBR) on patients diagnosed with RA from 2010 or later (the post 2009 group). See section 2.3.2 of the DSU report for further details. These data and the variance co-variance matrices were differentiated by those patients with severe RA and those with moderate-to-severe RA meaning that 20,000 hypothetical patients were now simulated with moderate-to-severe RA, instead of the 2000 simulated in the base case of the February 2015 report.

A hypothesis that was put to the Assessment Group by during the consultation phase of the DSU report was that the average HAQ reduction for those who obtain either a good or a moderate EULAR response would be greater given more recent treatment regimens than for the entire BSRBR population. This was conjectured to be because those with with less current treatment regimens may have more irreversible damage. The cut-off date of January 2010 was provided by the BSRBR. Sensitivity analyses have therefore been conducted changing these parameter values from those in the base case, which was an average HAQ reduction of 0.317 for those with a moderate EULAR response and 0.672 for those with a good EULAR response. The Assessment Group were provided with no robust data to support a greater HAQ reduction in this patient group but have arbitrarily used average HAQ reductions of 0.500 for those with a moderate EULAR response and 1.000 for those with a good EULAR response to explore the sensitivity of the ICER to this assumption.

4. Results

The only analyses conducted were those based on EULAR data being reported directly in the RCTs. The results provided in the February 2015 report did not support a clear difference between those produced by EULAR directly and those produced when ACR responses were mapped to EULAR responses. The direct mapping has less associated uncertainty in EULAR responses, although the evidence base is smaller and no results could be provided for subcutaneous abatacept.

The results are presented separately for those with severe RA (Population 2 in the NICE scope) and for those with moderate-to-severe RA (Population 3 in the NICE scope). Given the extremely high ICERs of approximately £300,000, for patients with severe RA who are cDMARD naïve (Population 1 in the NICE scope), no further analyses have been performed on this group.

No results for patients who cannot receive methotrexate (MTX) have not been calculated, although it is noted that the ICERs for this group were shown in the February 2015 report to be approximately £25,000 greater than for those who can receive MTX.

A summary of the results is presented in Table 1. The summary presents only the median ICERs from the range of mean values for each bDMARD strategies, This was undertaken as the efficacies and costs of the bDMARDs are relatively similar, and as such, attempting to definitively differentiate between the cost-effectiveness of bDMARDs is likely to be unwise. However, for information fully incremental analyses are presented after the summary. The base case scenario remains that as in the February 2015 report as currently it is not possible to identify within each latent class those people with the greatest HAQ progression.

No attempts have been made to ascertain a threshold level of HAQ progression whilst on cDMARDs that would be associated with median ICERs for bDMARDs of £20,000 or £30,000 per QALY. This is due to the fact that it is clear from the data within the DSU report that HAQ progression whilst on cDMARDs is unlikely to be linear over time. However, the exploratory analyses conducted are likely to be highly favourable to bDMARDs and as such provide an indication of the lower bounds of plausible ICERs for bDMARD strategies compared with non-biologic therapies.

Table 1: Summarised results: Median ICERs for all bDMARD strategies compared with the MTX alone strategy. Populations 2 and 3 who can receive MTX

	Base Case +				
	N/A (i.e. the Base case)	Assuming patients with the greatest HAQ progression can be identified (1)	Using the post 2009 population	Using the post 2009 population with assumed arbitrary greater HAQ decreases (2)	Assuming patients with the greatest HAQ progression can be identified and using the post 2009 population with assumed arbitrary greater HAQ decreases (1 and 2)
Population 2 (severe MTX – experienced)	£61,200	£44,700	£83,000	£65,800	£42,300
Population 3 (moderate MTX-experienced)	£75,000	£54,600	£92,900	£74,800	£47,900

All numbers rounded to the nearest £100

For definitions of 'patients with the greatest HAQ progression' and for the 'post 2009 population' refer to the main text

4.1 Results for a severe RA, MTX experienced population

Table 2: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a 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]	£ 61,239	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 58,969	£ 58,969
IFX + MTX	[redacted]	[redacted]	£ 59,530	Dominated
ADA + MTX	[redacted]	[redacted]	£ 62,948	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 61,084	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 62,664	Dominated
ETN + MTX	[redacted]	[redacted]	£ 61,497	£ 84,246

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £58,000 to £63,000.

Table 3: Deterministic base case results using EULAR data directly – selecting patients with the greatest HAQ progression and a 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]	£ 44,691	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 42,078	£ 42,078
IFX + MTX	[redacted]	[redacted]	£ 42,678	Dominated
CTZ + MTX	[redacted]	[redacted]	£ 44,222	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 45,367	Dominated
GOL + MTX	[redacted]	[redacted]	£ 45,192	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 45,030	£ 79,136

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £42,000 to £46,000.

Table 4: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, post 2009 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]	£ 85,402	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 80,980	£ 80,980
IFX + MTX	[redacted]	[redacted]	£ 82,977	Dominated
CTZ + MTX	[redacted]	[redacted]	£ 82,459	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 84,736	Dominated
GOL + MTX	[redacted]	[redacted]	£ 84,144	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 81,781	£ 88,572

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £80,000 to £86,000.

Table 5: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a severe, MTX-experienced, post 2009 RA population and assuming a 1.0 HAQ drop and 0.5 per moderate EULAR responder.

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 67,485	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 64,338	£ 64,338
IFX + MTX	[redacted]	[redacted]	£ 65,770	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 65,400	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 67,442	Dominated
GOL + MTX	[redacted]	[redacted]	£ 66,295	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 65,460	£ 74,763

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £64,000 to £68,000.

Table 6: Deterministic base case results using EULAR data directly – selecting patients with the greatest HAQ progression and a severe, MTX-experienced, post 2009 RA population and assuming a 1.0 HAQ drop and 0.5 per moderate EULAR responder.

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]	£ 40,124	£ 40,124
TCZ + MTX	[redacted]	[redacted]	£ 43,348	Dominated
IFX + MTX	[redacted]	[redacted]	£ 41,275	Dominated
ADA + MTX	[redacted]	[redacted]	£ 42,316	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 41,539	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 42,336	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 42,463	£ 70,109

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £40,000 to £44,000.

4.2 Results for a moderate-to-severe RA, MTX experienced population

Table 7: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate-to-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]	£ 75,040	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 72,794	Ext Dominated
IFX + MTX	[redacted]	[redacted]	£ 72,238	£ 72,238
CTZ + MTX	[redacted]	[redacted]	£ 74,579	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 76,333	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 76,181	Dominated
ETN + MTX	[redacted]	[redacted]	£ 75,791	£ 112,689

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £72,000 to £77,000.

Table 8: Deterministic base case results using EULAR data directly – selecting patients with the greatest HAQ progression and a moderate-to-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]	£ 54,373	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 51,222	£ 51,222
IFX + MTX	[redacted]	[redacted]	£ 51,581	Ext Dominated
ADA + MTX	[redacted]	[redacted]	£ 55,535	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 54,636	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 55,231	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 55,438	£ 105,588

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £51,000 to £56,000.

Table 9: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate-to-severe, MTX-experienced, post 2009 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]	£ 94,336	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 90,025	£ 90,025
IFX + MTX	[redacted]	[redacted]	£ 91,402	Dominated
ADA + MTX	[redacted]	[redacted]	£ 94,975	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 92,641	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 94,159	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 92,881	£ 117,039

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £90,000 to £95,000.

Table 10: Deterministic base case results using EULAR data directly – ERAS cDMARD HAQ progression and a moderate-to-severe, MTX-experienced, post 2009 RA population assuming a 1.0 HAQ drop and 0.5 per moderate EULAR responder.

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 76,099	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 72,978	£ 72,978
IFX + MTX	[redacted]	[redacted]	£ 74,248	Dominated
ADA + MTX	[redacted]	[redacted]	£ 76,950	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 74,807	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 76,424	Dominated
ETN + MTX	[redacted]	[redacted]	£ 74,789	£ 90,366

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £72,000 to £77,000.

Table 11: Deterministic base case results using EULAR data directly – selecting patients with the greatest HAQ progression and a moderate-to-severe, MTX-experienced, post 2009 RA population and assuming a 1.0 HAQ drop and 0.5 per moderate EULAR responder.

First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	Incremental CPQ
MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 49,214	Ext Dominated
ABT i.v. + MTX	[redacted]	[redacted]	£ 45,273	£ 45,273
IFX + MTX	[redacted]	[redacted]	£ 45,965	Dominated
ADA + MTX	[redacted]	[redacted]	£ 48,044	Ext Dominated
CTZ + MTX	[redacted]	[redacted]	£ 47,123	Ext Dominated
GOL + MTX	[redacted]	[redacted]	£ 47,933	Ext Dominated
ETN + MTX	[redacted]	[redacted]	£ 48,134	£ 83,468

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

It is seen that the ICERs of all the bDMARDs compared with the MTX strategy are in the region of £45,000 to £50,000.

5. Conclusions

The Assessment Group estimate that the cost per QALY gained for bDMARD strategies is in excess of £60,000 in a severe RA population who can receive MTX and approximately £75,000 in a moderate-to-severe RA population who can receive MTX. Based on the results presented in the February 2015 report it is expected that the ICERs would be higher for those who cannot receive MTX.

Currently implausible strategies that are predicated on being able to identify at initiation those patients with the greatest HAQ progression reduce the ICERS to in excess of £40,000 for the severe RA population and in excess of £45,000 for the moderate-to-severe population.

All of these ICERs have assumed that NICE's guidance on stopping bDMARD treatment at six months should there be no EULAR response is strictly followed. Data presented in the February 2015 report indicate that this is not / has not been adhered to, indicating that over 25% of patients who had no EULAR response at six months were still on treatment at 4.5 years, with the median treatment time being 319 days. The consequence of non-adherence is anticipated to be an increase in the ICER.

References

[1] Stevenson MD, 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

[2] Gibson L, Hernández Alava M, Wailoo A. (2015) Progression of disease in people with rheumatoid arthritis treated with non biologic therapies. Report by the Decision Support Unit. School of Health and Related Research, University of Sheffield