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# Abstract

## Objectives

Many algorithms exist for converting the Health Assessment Questionnaire (HAQ) score to utility in rheumatoid arthritis (RA). Different algorithms convert the same HAQ score to different utility values, and could therefore lead to different cost-effectiveness results. Our objective was to investigate the impact of different mapping algorithms within the same cost-effectiveness model.

## Methods

We rebuilt an existing economic model which had previously been used for estimating the cost-effectiveness of second-line biologics in RA. We reviewed the literature to identify algorithms which converted HAQ to utility and incorporated them into the model. We compared the cost-effectiveness results using different algorithms, exploring the reasons behind the different results and the potential effect on reimbursement decisions.

## Results

We identified 24 different algorithms which estimated utility based on HAQ score, age, gender and pain. The incremental cost-effectiveness ratio (ICER) for rituximab versus disease modifying anti-rheumatic drugs (DMARDs) varied between £18,407/quality adjusted life year (QALY) and £32,039/QALY, which we speculate could have changed the recommendations made by the National Institute for Health and Care Excellence.

## Conclusion

Using different algorithms to convert HAQ to utility affects the cost-effectiveness of second-line biologics for the treatment of RA. Using different algorithms in economic modelling for RA could lead health technology assessment bodies to make different reimbursement decisions.

# Introduction

Many different algorithms have been used to convert the Health Assessment Questionnaire (HAQ) score to utility in rheumatoid arthritis (RA). These algorithms have been produced both in studies of their own merit, and for use within economic modelling. In order to calculate a cost per quality-adjusted life year (QALY), economic models must estimate QALYs, which require a measure of utility. Utility is anchored between 0 and 1, and is often calculated from generic preference based measures such as the EuroQol Five Dimension (EQ-5D) questionnaire. However, such measures are not routinely included in clinical trials for RA, whereas the HAQ is a mandated outcome [1].

The National Institute for Health and Care Excellence (NICE) Reference Case in the Guide to Methods of Technology Appraisal states that where EQ-5D data is not available, mapping may be used [2]. Recent reviews of the use of mapping have found the validity of algorithms to be variable [3] and the documentation supporting the use of algorithms within NICE submissions to be generally poor [4]. Since different mapping algorithms produce different utilities from the same data and therefore influence cost-effectiveness results within the same economic model, it is unsurprising that the NICE Reference Case therefore also states that “Sensitivity analyses to explore variation in the use of the mapping algorithms on the outputs should be presented”[2]. However, extensive sensitivity analysis is not routinely incorporated into economic evaluations and submissions to NICE. Indeed, in the ongoing NICE multiple technology appraisal (MTA) for first line biologics for the treatment of RA, most manufacturers and the assessment group considered only two mapping algorithms in their analyses, with one manufacturer considering four [5].

It is unclear from the NICE Reference Case and guidelines for submission to other health technology assessment (HTA) [2] [6] [7] [8] bodies to what extent sensitivity analysis on mapping algorithms should be conducted (if at all) – whether it is sufficient to include one additional algorithm or whether all relevant algorithms should be identified and included. While the latter option is no small undertaking, the former option still leaves open the risk that the manufacturer (or indeed assessment group) could tactically choose those mapping algorithms that lead to the most favourable results. There is therefore a need to understand the impact of investigating a range of mapping algorithms, at least within those disease areas such as RA where it is understood many exist.

We investigated the influence of utility mapping algorithms on the cost-effectiveness of second line biologics for RA. In 2010, NICE conducted a MTA of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a tumour necrosis factor (TNF) inhibitor [9] (second line biologics). We rebuilt the economic model used by the assessment group [10] and investigated the impact different mapping algorithms had on the cost-effectiveness results.

## Methods

### *Model rebuild*

We firstly rebuilt the model used by the assessment group in TA195 [9], using a detailed description. The model is a version of the Birmingham RA Model (BRAM), and is an individual patient sampling model: a cohort of virtual patients is simulated and these patients then receive a sequence of treatments [10]. The treatment sequence begins with a biologic (adalimumab, etanercept, infliximab, rituximab or abatacept) and is followed by five disease-modifying anti-rheumatic drugs (DMARDs). Each treatment is associated with a change in HAQ score, which is sampled from a distribution for each patient. The time each patient spends on each treatment is also sampled from a distribution. All of the inputs for the model were provided, and the structure of the model was well detailed [10]. The assessment group model was built in Borland Delphi, but we used Simul8, which facilitates discrete event simulation. We compared the base case and scenario analysis results for our model with those published.

### *Adapting the model to include a new variable*

We incorporated pain as a new variable into our model, which required that we find inputs for the effect on pain measured on the visual analogue scale (VAS) for each treatment. Hernández Alava et al, who developed several statistical models to relate HAQ score to EQ-5D, found that “the inclusion of pain measured on a VAS vastly improved the models.” [11] The change in pain, as measured on the VAS, was not reported in the model description from which we rebuilt the model [10], but the papers which reported the effects of each treatment on HAQ were referenced. We followed up these references, and found values for the effect of each biologic on pain measured on the VAS. The assessment group in TA195 identified the HAQ change for DMARDs when used before biologics, and assumed the change in HAQ would be halved when used after biologics [10]. We identified the change in pain as measured on the VAS from the same sources, and so continued the assumption that efficacy would be halved, by halving the change in pain as measured on the VAS. The change from baseline to month 6 in pain measured on the VAS for each treatment is shown in Table 1.

[Table 1 to go here]

### *Identifying mapping algorithms*

We identified 24 utility mapping algorithms which could be used to convert HAQ scores into EQ-5D. We chose EQ-5D as an outcome as it is NICE’s preferred measure of EQ-5D in adults [2]. These mapping algorithms could include only HAQ score, age, gender and pain measured on the VAS. We could not consider algorithms which included variables not included in the BRAM such as duration of disease, disease activity score (DAS) or American College of Rheumatologists 20/50/70, or HAQ domain scores. We identified mapping algorithms for inclusion in the model in four ways:

1. The description of the assessment group model [10] reported the mapping algorithm used in their base case as well as three used in the manufacturer submissions [10], [12], [13].
2. Hernández Alava [11] cited six existing mapping algorithms [14], [15], [16], [17], [18], [19] and created four original models. We followed up the cited mapping algorithms and included the two which used relevant variables [15], [19].
3. We searched the literature using Medline via Ovid, and identified 10 new algorithms (23rd September 2012) [20], [21], [22], [23], [24], [25], [26], [27], [28], [29].

4. We searched the health technology assessment (HTA) journal database for technology appraisals within RA, and followed up the mapping algorithms used in these. This identified three new algorithms [30], [31], [32].

The PRISMA diagram for the Medline search is shown in Figure 1 (search strategy is available in supplementary material). In total from the four search methods, two mapping algorithms were excluded as the outcome was not EQ-5D and eight because they included additional variables not considered in our model.

[Figure 1 to go here]

We incorporated the 24 identified algorithms into our model and ran the model for each algorithm. Simul8 uses the same random numbers each time, and so essentially simulates the same patients for each treatment, and for each algorithm. We then judged the ICERs against the £20,000-£30,000/QALY thresholds considered by NICE to determine whether using different algorithms in TA195 could have led to different recommendations. The mapping algorithms are shown in Table 2. Algorithms which convert HAQ to EQ-5D using a linear regression represent the most commonly used algorithms in economic modelling for RA. Algorithm 1 is the algorithm which was used in the assessment group model for TA195.

[Table 2 to go here]

## Results

### *Results of the model rebuild*

Our rebuilt model reported similar results to the published model (Table 3). The costs and QALYs for each treatment lay within the 95% confidence intervals of the published model, indicating that our results were not statistically significantly different to those considered in TA195 [10]. We repeated a selection of the scenario analyses reported [10] and found our change from base case to be similar to each scenario in direction and magnitude. We were therefore satisfied that our model was a sufficiently accurate replication that the changes in our results due to the mapping algorithms would be similar in the published model.

[Table 3 to go here]

### *Results from different mapping algorithms*

The QALYs produced for each treatment varied when different mapping algorithms were used. The QALYs compared to DMARDs are presented in Figure 2 for adalimumab, etanercept, infliximab, abatacept and rituximab. The QALYs generated by the DMARDs strategy ranged dramatically from 2.13 to 5.65 (see table in supplementary material), and the relative increase in QALYs for rituximab versus DMARDs varies between 108% and 128% (and similarly for the other biologics).

[Figure 2 to go here]

Rituximab consistently dominates adalimumab, etanercept and infliximab as it results in lower costs (which are not influenced by the choice of mapping algorithm) and more QALYs. The two comparisons we are therefore most interested in are rituximab compared to DMARDs and abatacept compared to rituximab. In order to understand the impact of the different algorithms, the results for these comparisons are presented separately in Figure 3.

[Figure 3 to go here]

When applying a cost-effectiveness threshold of £20,000, it can be seen from Figure 3 that rituximab would only be cost-effective using utility mapping algorithms 21 [11], 22 [11] and 23 [11]. However, NICE approved rituximab with an ICER of £21,100, so we instead consider a cost-effectiveness threshold of £30,000. Two things are immediately obvious:

- Abatacept is never cost-effective compared to rituximab (as established previously)
- Rituximab is cost-effective using the majority of utility mapping algorithms, with the exceptions being 9 [23], 17 [26] and 20 [29]

We therefore investigated why the ICER for rituximab compared to DMARDs is particularly high using algorithms 9, 17 and 20.

Algorithm 9 is a linear model, of the same form as algorithms 3-11:

$$EQ - 5D = a - b \times HAQ$$

Coefficients  $a$  and  $b$  are lower for algorithm 9 than for any other linear model. If coefficient  $a$  decreases, the QALYs produced for both rituximab and DMARDs decrease, and the incremental difference decreases, leading to a higher ICER. If coefficient  $b$  is lower, less weight is given to the HAQ score and so again the incremental QALYs decrease, leading to a higher ICER.

Algorithm 17 assigns EQ-5D scores to HAQ health states. The HAQ health states are the same as those used in algorithm 16, which shows rituximab to be cost-effective at a threshold of £30,000/QALY. The EQ-5D scores in algorithm 16 are from a population in Sweden, whereas those in algorithm 17 are from a population in the UK.

The EQ-5D scores are generally higher for the UK population than for the Sweden population, with the exception of the  $1.1 \leq \text{HAQ} < 1.6$  health state. The fall in utility from patients moving into this state is much higher in the Sweden population than in the UK population, leading to a much greater improvement in utility using the values from the Sweden population than from the UK population. In turn this leads to a greater difference in QALYs between the rituximab and DMARDs, hence the higher ICER for algorithm 17 than algorithm 16.

Algorithm 20, like algorithms 13-19 uses HAQ health states. However, algorithm 20 has the fewest health states. It appears that using fewer health states does not sufficiently differentiate between the benefit of the treatments for rituximab to be cost-effective at a £30,000/QALY threshold.

### *The impact of including pain in the utility algorithm*

In algorithms 1-20, etanercept consistently produces more QALYs than infliximab (average difference 0.09, range 0.07 to 0.10). The improvement in HAQ score is the same between the treatments, as is the long-term time to discontinuing treatments (mean 4.06 years). The only difference in efficacy between the treatments is the short-term probability of discontinuing treatment, which is 5.2% at 13 weeks for etanercept, and 23% at 16 weeks for infliximab. It is the short-term probability of discontinuing treatment which drives the difference between their effectiveness when pain as measured on a VAS is not incorporated. When pain as measured on a VAS is incorporated into utility mapping algorithms 21-23, the QALYs produced by etanercept become almost identical to those by infliximab, as seen by the overlapping points in Figure 2. This demonstrates that the inclusion of pain measured on a VAS could potentially change the ordering of effectiveness of interventions and



therefore change the interventions lying on the cost-effectiveness efficiency frontier. This is investigated further in sensitivity analysis.

### *Sensitivity analysis*

We used fractional factorial sensitivity analysis to investigate the uncertainty around the change in pain as measured on a VAS for each treatment. We used algorithm 24, the mixture model, because this was found to outperform the other models which also incorporated pain [11]. The QALYs for each biologic treatment are calculated when the mean pain decrease, as measured on a VAS, is set to either the 'low' value (5.48) or the 'high' value (29.00). The results are plotted on a cost-effectiveness plane in Figure 4. For each biologic, the QALYs using the 'low' value are the leftmost of the pair of points. The costs do not change as these are not related to pain or utility. Figure 4 demonstrates that:

- Abatacept is the most effective treatment in all scenarios except where its change in pain is set to the low value, and rituximab's is set to the high value. In this case, rituximab dominates abatacept. Where rituximab and abatacept are both set to the low values, both set to the high values, or rituximab set to the low value and abatacept to the high value, both lie on a cost-effectiveness efficiency frontier, and the other biologics are either dominated or extendedly dominated.
- At a threshold of £20,000/QALY, none of the biologics are cost-effective compared to DMARDs (all points lie to the left of the willingness to pay threshold line)
- At a threshold of £30,000/QALY, rituximab is the only cost-effective treatment compared to DMARDs regardless of whether its change in pain is set to the high or low value
- Abatacept compared to rituximab has an ICER of over £30,000/QALY on all of the possible frontiers.

[Figure 4 to go here]

Additionally, to explore whether the presence of correlation between the pain and HAQ outcomes could affect these conclusions we considered a simple sensitivity analysis in which the improvement in pain was correlated with the improvement in HAQ score. We calculated the sampled HAQ improvement as a proportion of the mean HAQ improvement, and multiplied this by the mean improvement for pain measured on the VAS, to give the sampled improvement for pain. We found

that although this did change the ICERs for rituximab compared to DMARDs and abatacept compared to rituximab, the difference was relatively small and did not cross the cost-effectiveness thresholds. Rituximab compared to DMARDs increased from £22,000/QALY to £26,000/QALY and abatacept compared to rituximab decreased from £115,000/QALY to £103,000/QALY.

## Discussion

Our analysis demonstrates that the different algorithms for mapping from HAQ to utility lead to different cost-effectiveness results for second line biologics. The algorithm (1) used in TA195 leads to an ICER for rituximab versus DMARDs of £23,000/QALY in our analysis, but we have demonstrated that using a different mapping algorithm could have increased the ICER above £30,000/QALY.

It is a strength of this research that the results from our rebuilt model are so close to those published. This indicates that we have recreated the model accurately (small differences are due to different random number and the inherent complexities in recreating someone else's work). This means that the results from our model would likely have also applied to the model used in TA195.

Our results are consistent with existing studies, but this analysis emphasises the importance of identifying the most appropriate mapping algorithm. The need to determine which algorithm is most appropriate raises questions and leads to discussion as to how this is to be decided. It should be noted that our aim was not to determine which algorithm is most appropriate, but to investigate whether this is an area modellers and decision-makers should consider important. Historically in RA modelling, it has been assumed that the simple linear regression models are adequate for relating HAQ to utility, but recent research has highlighted that additional variables and more sophisticated modelling techniques lead to more realistic distributions of EQ-5D [11]. We therefore question whether given this knowledge, it can continue to be assumed that the simple linear regression models using only HAQ are adequate. Linear regression models remain the most commonly used methods of mapping from HAQ to utility, and indeed were used in all of the manufacturer submissions in the recent NICE MTA for first line biologics (ID 537) [5].

The mapping algorithms reported by Hernández Alava et al [11] caused some of the most drastic changes to the cost-effectiveness results. Although the results would have been unlikely to change NICE's decisions (because the ICER for rituximab versus DMARDs is lower than using the algorithm

from TA195 [10], and the ICER for abatacept versus DMARDs is far above commonly-accepted thresholds), they show a decrease in the ICERs for both rituximab versus DMARDs and abatacept versus rituximab. This is because they show a greater difference between the efficacies of the treatments, which is likely to be due partially to the incorporation of pain as measured on a VAS. Brazier et al state that “the strength of the mapping algorithm depends on the degree of overlap between the descriptive systems” [33]. Pain, one of the most heavily weighted items in EQ-5D, is not included in the HAQ summary score, so it is unsurprising that additionally including pain in the mapping algorithms improves the fit of the models. An algorithm which includes pain and therefore creates a greater degree of overlap is theoretically a stronger algorithm, and arguably more appropriate for use within economic modelling. We therefore support the recommendations by Hernandez et al [34] that in RA, QALYs should be estimated from the HAQ and pain. This extends outside of RA, where there has been much discussion regarding whether generic preference based tools are insensitive in some disease areas [35] [36]. We suggest researchers constructing mapping algorithms should also pay attention to whether the disease specific measure being used to map to those generic measures are able to capture all aspects of the disease which may impact directly or indirectly on the domains of the generic instrument being used [4].

Our incorporation of pain has its limitations. Firstly, it is plausible that there is a relationship between pain and the HAQ score; disease severity which leads to pain could also feasibly limit functional capacity; and our model does not allow for this covariance. However, our sensitivity analysis indicated that this relationship is unlikely to dramatically change the results.

Secondly, to accurately model pain, we would ideally have performed a formal systematic review and meta-analysis to find the most appropriate values. However, the aim of this study was not to update the efficacy evidence base, but to investigate what the impact of other algorithms would have been in the NICE appraisal. For this reason, it was appropriate to use only the efficacy sources available at the time and considered in TA195.

We have demonstrated that selecting certain mapping algorithms could determine whether a treatment is cost-effective or not at a given threshold. With this knowledge, manufacturers could therefore potentially strategically select mapping algorithms for use in submissions. We support NICE’s request for sensitivity analysis using alternative mapping algorithms [2], and recommend that

other HTA bodies should make similar demands. We suggest that the decision of whether it is necessary to include the full array of mapping algorithms depends somewhat on the validity of the different mapping algorithms - in this case it appears that the algorithms developed by Hernandez are superior, and so the additional inclusion of older, less sophisticated methods is unnecessary. We would also suggest that where multiple mapping algorithms do exist, justification should be provided for the choice of algorithm both in the base case and in sensitivity analysis.

To our knowledge, no other studies of this scale exist comparing the impact of implementing different HAQ to utility mapping algorithms in RA. It has therefore been difficult to compare our results to existing literature. However, it should be considered a strength of our analysis that we present an original exploration in a topical area.

Our research has demonstrated that the algorithms used to convert HAQ to utility affect the cost-effectiveness results of second line biologics in RA. It is reasonable to assume that the mapping algorithms could also influence cost-effectiveness of treatments for RA in all lines. Furthermore, using different algorithms could lead health technology assessment bodies to make different decisions regarding reimbursement.

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