NICE Decision Support Unit responses to comments received from consultation on DSU Report "PROGRESSION OF DISEASE IN PEOPLE WITH RHEUMATOID ARTHRITIS TREATED WITH NON BIOLOGIC THERAPIES"

Allan Wailoo, Laura Gibson, Monica Hernández, Matt Stevenson

School of Health and Related Research, University of Sheffield.

29th April 2015

RESPONSES TO CONSULTEE COMMENTS, GROUPED BY THEME.

This document sets out responses to key issues raised in the consultation exercise. It does not provide a point by point response to every issue raised but instead groups comments made recurrently together under general themes. It should therefore be read in conjunction with the original consultee comments.

1. Issue of using data from a broader population of patients with RA and making implications for subgroups versus using only data from those subgroups (BSR, Pfizer, Roche)

As pointed out in the DSU report, the baseline characteristics of the ERAS population of patients (and other inception cohorts) is not equivalent to the population recommended from treatment with biologics in the UK NHS. However, ERAS and the other selected datasets follow patients over a very long period, during which some of those patients develop disease and fail other treatments such that they would be eligible for biologic therapy either under current NICE guidelines, or under proposed extensions to those eligibility criteria.

For example, whilst the DSU reports that for those observed to take a 3rd DMARD in the ERAS dataset 25% had severe active disease (DAS>5.1) at this first observation, a much higher proportion have a DAS>5.1 at some future stage. In addition, because this observation occurs after the beginning of the 3rd DMARD, many patients will have achieved some treatment response and therefore have a reduced level of disease activity but would have been eligible for biologics at failure of the 2nd DMARD.

Furthermore, we undertake sub-analyses conducted solely on those patients starting their third DMARD to validate the findings of the analyses conducted on the full patient sample.

Pfizer compare the baseline characteristics of the BSRBR with the baseline of ERAS. However, the variability in the BSRBR population is ignored. For example, whilst the mean disease duration of the severe active disease population treated with biologics in the BSRBR is 9.4 yrs, this is associated with a standard deviation of 9.3 yrs i.e. many individuals are placed on biologics almost immediately after diagnosis. Whilst there may be significant

differences in the mean characteristics of the ERAS cohort at baseline and the biologics registry data, this fails to recognise that there is also significant overlap.

2. Analysis of the CORRONA dataset invalidates the findings in the DSU report (Abbvie).

The CORRONA analysis conducted by Abbvie has only 5 years of follow up making it non comparable with the datasets identified and selected for use in the DSU analyses. Abbvie provide no details either of the sample used or of the analyses undertaken to enable a judgement to be made about their claims.

3. "Attrition" is a bias that disadvantages the cost effectiveness of biologic therapies. (BSR, Abbvie, Roche)

There are many reasons why individuals withdraw from the datasets that were selected for use in the DSU analysis. In addition, the DSU undertook extensive analysis to model the effects of attrition on the estimates:

i) Remission. Patients in remission may either choose to withdraw from these studies or, in many of them, would automatically be withdrawn because they would no longer be under the care of the rheumatologist (a condition for maintained study eligibility). Where patients withdraw because of remission, the remaining observed patients have a higher HAQ than the true patient cohort. That is, any existing bias would cause the observed mean HAQ to be higher.

ii) Death. Patients that die are of course withdrawn from the analysis. However, the rate of HAQ progression that is required for the Assessment Group (AG) model is the rate of HAQ progression for those patients that remain alive, because patients are withdrawn from the TA model as they die. Withdrawal due to death is therefore not an inherent bias given how the data are subsequently used in the cost effectiveness model.

iii) Disease worsening. If patients experience a worsening in function, and therefore choose to withdraw from the study at a rate that is greater than the rate of withdrawal for other patients, then this would result in a bias in the HAQ progression rate downwards. That is, any existing bias would cause the observed mean HAQ to be lower.

4. Patients most likely to drop out are those that would be eligible for biologics rendering the methods for dealing with missing data void (Abbvie, 1.2.4)

There seems to be a misunderstanding of the analysis that was conducted, leading to this claim. The DSU conducted a series of analyses which investigate the impact of alternative methods for explicitly modelling the effect of dropout in the ERAS dataset. The approach using the Roy-Muthen method identified three latent dropout classes within each of the four previously existing latent classes of HAQ growth. Abbvie claim that the results show that those patients most likely to drop out early in the follow up period for ERAS are most likely to belong to dropout class 1 (correct as shown in Table 28 of the DSU report) and that these are those with the highest baseline HAQ and most likely to be those eligible for biologics.

This is incorrect because dropout class 1 is present in each of the four latent classes i.e. both those with the highest baseline HAQ, the lowest baseline HAQ and those in between (see Figure 25).

5. Extrapolating the effect of disease duration beyond the ERAS baseline characteristics underestimates HAQ progression (Abbvie 1.3.1)

Disease duration (DD) in the latent class models affects the probability of an individual being allocated to each of the four classes. We find a longer DD increases the probability of an individual being in the two classes with the highest HAQ. Our estimates using ERAS already allocate individuals to these classes with a very high probability for the severe active disease group, so there is little scope for bias from extrapolation beyond the observed values in the dataset to cause an increase further. In addition, if any bias exists it could operate in either direction and therefore lower the probabilities of being in these top classes.

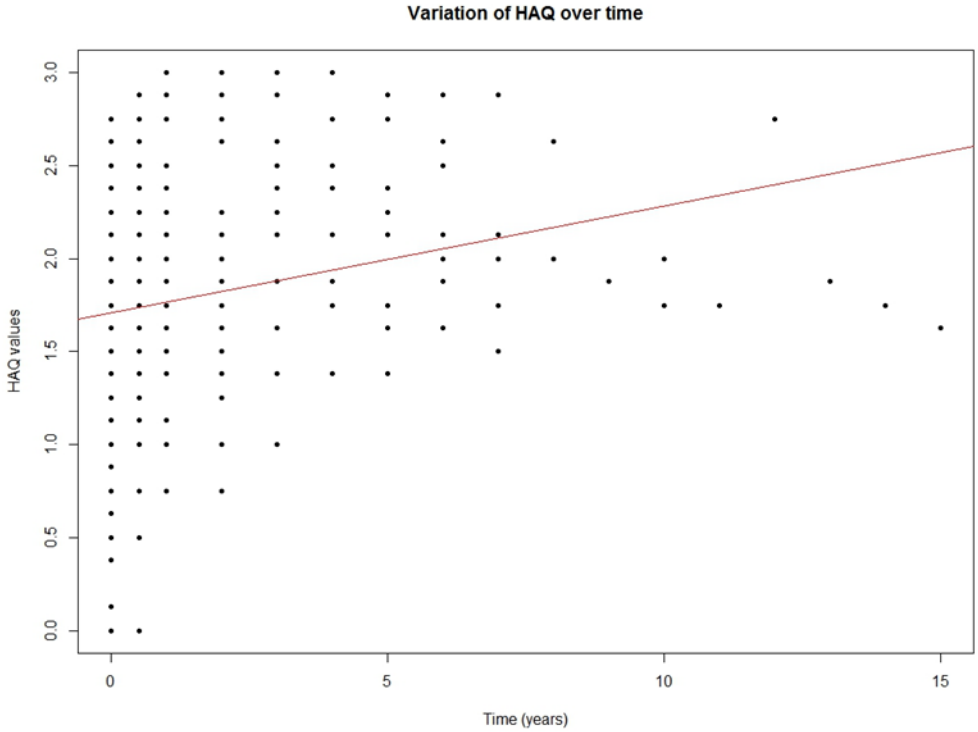
It is also the case that there is a further assumption made in favour of a high rate of HAQ progression in the implementation of these results in the AG model. That is, that the rate of progression is taken from year 1, even for those with very long disease durations, because this is the point from which all of the 4 HAQ trajectory classes are observed to experience the most rapid period of worsening.

6. Additional analysis of ERAS data (BSR)

The BSR appendix provides details of additional analyses conducted on the ERAS database. The claim is that the analysis supports a high rate of HAQ worsening at a linear rate. We disagree with the main interpretation of the findings. Figure 1 below is from the BSR submission:

The solid (red) line indicates the linear regression model that was fitted to HAQ data for a severe DAS patient subgroup. We suggest that the analysis reveals the linear relationship simply does not fit the presented data and that the true relationship is clearly non-linear.

Figure 1: Analysis of HAQ in severe DAS group using data from ERAS (BSR analysis Appendix)



7. *Additional analysis from Norton et al (Pfizer)*

Reference is made to a conference abstract with first author Norton with the claim that this substantiates that HAQ progression is linear and at a higher rate than the 0.045 HAQ per annum previously used in NICE appraisals. The analysis used data from ERAS and ERAN combined. We dispute the interpretation of the results for the following reasons:

i) The data were analysed as subgroups based on the mean DAS for each individual over the follow-up period. Therefore, the HAQ rate estimated for "severe" patients, for example, relates only to those patients that maintained a severe DAS. It does not include those patients that achieved a response to ANY of the treatments they received (including both non biologic DMARDs and surgery) and moved to a lower DAS category. The rates are therefore not relevant to the decision problem.

ii) A linear model was fitted to the data i.e. a linear worsening over time was imposed on the data with no consideration of alternative functional forms.

iii) The estimated rate of progression in the early years of DMARD therapy in the DSU model was substantially higher than the rate of 0.064 reported in the Norton abstract for those with moderate – severe DAS.

iv) The estimated rate of HAQ progression for patients on biologic therapy was 0.019 in this study. The AG model assumes zero HAQ progression on biologics.

8. The importance of avoided surgery as a benefit of biologics (NRAS, BSR, Pfizer)

Several stakeholders highlight the importance of avoided surgery as a key benefit of treatment for RA that is associated with treatment with biologics. Estimates are provided of the reduction in joint replacement surgeries attributable to biologics. The AG model explicitly incorporates the costs of avoided surgery into the model. The only means by which the benefits of surgery can be reflected is via its impact on HAQ. The HAQ trajectories reflected in the DSU report are a reflection of treatment in the absence of biologics, which is acknowledged by stakeholders to include widespread use of surgery, particularly in those patients that have a high degree of functional disability and pain (i.e. those with a high HAQ). Surgery is known to a generally effective intervention for the improvement of function and pain and it is this treatment which, in part, is likely to lead to a slowing and potential fall in the level of HAQ for patients relevant to his appraisal. Contrary to claims that this biases the estimates of HAQ progression, this in fact is a compelling reason for the observed trajectories.

9. Suggested alternative modelling approach using piecewise regression (BMS)

The DSU reports replication of the methods used in the original assessment report based on the publication by Norton et al and an alternative modelling approach (auto-regressive latent trajectory – ALT). The latter is a much more flexible approach than piecewise regression and was found to estimate the J-shaped HAQ data very well. Our view is that the suggested sensitivity analysis and confirmation of the HAQ trajectory is accomplished very well by the approaches reported in the DSU report.