Comments on the technical content of the DSU Report and the addendum to the Assessment Report on HAQ progression

The DSU report (2) from members of the Assessment Group provides additional evidence to support the rationale behind the approach to HAQ progression adopted in the Assessment Group's model, which is consistent with additional publications with their collaborators. This is particularly important given the Assessment Group's findings (1) that a key variable in determining cost effectiveness is how HAQ progression is modelled (1-p04#). In this context, the impact of different models of HAQ progression should be considered in sensitivity analyses. However, neither the DSU report, or the related AG report on the impact of the DSU report (3), properly address how different approaches might influence the conclusions, namely:

1. HAQ progression as relative scores versus absolute scores

The DSU report highlights the potential value of considering four latent class growth models which segregate according to DAS score at baseline. However, they have also shown in work with their collaborators that the failure to reduce high HAQ scores correlates with increased risk of mortality (6). This is part of the argument that absolute HAQ scores are important yet the AG model appears to use only relative changes in HAQ scores

(1-380#) "*Rather than use the model predictions for absolute HAQ values, we used the model to predict change in HAQ*."

Proposal: Sensitivity analyses comparing absolute HAQ values versus relative change in HAQ scores

2. Time frame

The DSU report and the AG findings risk extrapolating beyond the time frame of the data.

(2-p3#) "The cost effectiveness (CE) model requires estimates of HAQ progression over a patient's lifetime from the point at which they would be eligible for biologic therapies"

(1-380#) "Where extrapolation was used beyond the period for which data were available i.e. beyond year 15, we assumed zero HAQ progression"

"it is at these long extrapolations beyond 10 years where there is evidence that the model may under-predict HAQ worsening, even within the period covered by the data"

The study cited (5) examines mortality risk up to seven years through 2006, too early to establish the potential impact on mortality of a change in HAQ due to bDMARDs.

Proposal: Sensitivity analyses for different time frames for example 10, 15, 20 years to determine the uncertainty resulting from this extrapolation

3. Uncertainty

Relevance to Patients of Particular Interest

It is unclear how the DSU report relates to patients of particular interest i.e. those who are eligible for biologic therapies (which under current NICE Guidance is having failed two DMARDs and having a high Disease Activity Score (DAS) since they appear to report insufficient data to analyse the clinical group of particular interest i.e. cases that had failed two DMARDs and had severe active disease i.e. DAS>5.1.

(2-69#) … *to limit the analysis of data only to those patients that meet, or more closely meet, the criteria for receipt of biologic therapies. We found that there were insufficient data for analyses where samples were restricted to those that had failed two DMARDs and also had a DAS>5.1.*

Potential impact of small, clinically relevant differences between biological and conventional DMARDs

Neither the DSU report nor the addendum examine whether the conclusions on cost effectiveness are vulnerable to small, clinically relevant differences between biological and conventional DMARDS.

Proposal: Sensitivity analyses to examine whether small, clinically relevant differences in key variables for bDMARDs versus cDMARDs might affect cost-effectiveness; for example:

i. HAQ progression (4)

ii. Disease remission

iii. Dose reduction or withdrawal

iv. Mortality – particularly cardiovascular mortality

This is particularly important in a complex model where it is difficult to see what is going on "under the bonnet".

Proposal: Use the model to show how clinically effective an agent needs to be for key variables such as HAQ progression and mortality to be cost effective

References

(1 aka 1b) Stevenson M, .. Hernandez M, .. Wailoo A. 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. *Health Technol Assess*

(2) Gibson L, Hernandez M, Wailoo A. DSU Report: Progression of Disease in Rheumatoid Arthritis Treated with Non-Biologic Therapies. Report by the Decision Support Unit Feb 2015.

(3) Stevenson M and Wailoo A. Assessment Group Report: Assessing how the results from the DSU report on HAQ progression affect the cost per QALY gained ratios

(4) Michaud K, Wallenstein G, Wolfe F. Treatment and non-treatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. Arthritis Care Res (Hoboken). 2011 Mar;63(3):366-72. doi: 10.1002/acr.20405. Epub 2010 Nov 15.

(5) Michaud K, Vera-Llonch M, Oster G. Mortality risk by functional status and health-related quality of life in patients with rheumatoid arthritis. J Rheumatol. 2012 Jan;39(1):54-9. doi: 10.3899/jrheum.110491. Epub 2011 Nov 15.

(6) Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, Tosh J, Lunt M, Davies R, Young A, Verstappen SM. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014 Oct;44(2):131-44. doi: