BSR response to:

Multiple Technology Appraisal (MTA) Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) [ID537]

We are grateful to NICE for providing the opportunity to comment on the technical content of the DSU Report and the addendum to the Assessment Report on HAQ progression. In our response to the DSU report and related addendum, BSR will comment on several aspects that we feel have not been fully addressed. These will cover:

- Background and general comments
- Estimation of costs of therapies
- Estimation of HAQ progression on cDMARDs
- Derivation of health utility scores from HAQ score
- Discount rates and the changing financial environment of biologic therapies in the UK
- Fairness of the assessment process
- Moderate disease and stopping rules

Background and general comments

Rheumatoid arthritis (RA) is a complex, progressive, destructive disease with higher rates of morbidity and mortality than non-RA patients, often related to poorly controlled inflammatory disease. Failure of conventional disease modifying anti-rheumatoid drugs (cDMARDs) has a significant impact on patients (increasing pain, disability and loss of work) and the NHS (high costs associated with health service utilisation, such as joint replacement surgery and inpatient activity associated with co-morbidity development). The introduction of the biological therapies (bDMARDs) assessed in the DSU report has led to improved quality of life for patients and reduced opportunity costs in the NHS. Patients with RA would previously have had little therapeutic option after failure of cDMARD without biologic treatment, progressing inevitably to end-stage joint disease, joint replacement surgery, increasing disability, morbidity and social care utilisation.

The advent of bDMARDs in the management of RA has been associated with a paradigm shift in the management of this previously progressive and destructive disease. It is now unusual to see patients with progressive disability and joint deformity, and there is evidence of a reduction in inpatient treatment and orthopaedic surgery in patients with RA since these compounds were first approved by NICE (see below). Using an average medical bed day cost it is calculated that the opportunity cost of introducing biological therapies in 1999 could be around £1,497,422,395 b and the opportunity cost of RA associated reduction in hip and knee replacement surgery £22,296,479. RA associated hand surgery has practically been eliminated and the opportunity cost is currently being calculated. These factors have not always been fully accounted for in appraisals of the cost effectiveness of bDMARDs. Biological therapies (including tumour necrosis factor inhibitors (TNFi)) are therefore an established and essential component of the modern management of severe RA since NICE approved the use of the first available TNFi in RA in 2002. All TAs have found the use of biologic drugs to be cost effective after failure of cDMARDS and also after TNFi failure. The current NICE guidelines on the management of RA (CG79) and the related technology appraisals (TA130, TA195) recommend the use of bDMARDs in patients with severe, active disease who have failed to respond to cDMARDs.

The cost effectiveness of optimal management of early RA treating to a target of remission has been studied. The 'DREAM' study found that when TNFi are included in clinical pathways, treating to

remission dominates 'usual care' within three years, emphasising the economic benefit of including bDMARDs when other aggressive therapy has failed *(Vermeer M et al. BMC Musculoskeletal Disorders 2013;14:350)*. Although it may prove difficult to model such pathways from current data, we consider best practice for the management of RA is to treat to a target of remission with clinical protocols that include biologic drugs.

We also note that since the last committee meeting on this current appraisal, there have been changes in the funding of branded drugs. The PPRS 2014 has capped the NHS budget so increasing the use of biologic drugs in RA would not increase direct NHS costs. We consider that the effect of PPRS 2014 on opportunity costs needs to be taken into account by the appraisal committee. In addition, although we recognize that social costs are not estimated by NICE in MTAs, the modern management of RA, aiming for a target of clinical remission with protocols that include biologic drugs, has had a wider social impact for our patients. We would urge NICE to recognize that effective management of RA, utilising bDMARDs where appropriate, has drastically reduced the impact of the disease on a patient's ability to work, care for their families and themselves, thereby reducing social care and welfare costs and increasing productivity and work-related benefits.

Estimation of costs of therapies

We note the DSU has estimated costs of the interventions based on previous TAs, but we wish to highlight several potential inaccuracies that may influence the overall costs of cDMARDs, bDMARDs and palliative care. For example, it is estimated that 10% of subcutaneous injections of bDMARDs would be administered by District Nurses, an estimate derived from TA247. We feel that this is an overestimate and will vary significantly depending on hand function (which is well preserved in patients treated earlier, compared to historical pre-biologic cohorts) and device used (TA247 concerned s/c tocilizumab, administered using a more traditional needle and syringe device) , adding unfairly to the costs of bDMARDs.

Similarly, we are concerned that monitoring costs for methotrexate (MTX) have been allocated equally to bDMARD and cDMARD cohorts, with substantial costs attributed to monthly hospital outpatient attendances for MTX monitoring (£1700 per year). Whilst this may be accurate for patients who are failing to respond to MTX, it is not true for patients receiving bDMARDs who may be attending no more than twice a year, and therefore overstates the costs of bDMARD monotherapy. Similarly, no allowance is made for patients who undergo blood monitoring in primary care, although we accept this is likely to affect both cohorts equally.

We also draw attention to the apparent minimal financial cost assigned to the care of patients who would progress to palliative therapy, if bDMARDs were not used. This has been estimated as the cost of drug therapies (e.g. gold, leflunomide) only, with no attempt at assigning a true cost to the NHS of caring for a patient with progressive, destructive joint disease who does not have access to bDMARDs. Such costs need to reflect the increased health care utilisation incurred by the NHS when managing patients with RA who do not respond to cDMARDs. These costs should reflect the increased rheumatology outpatient utilization, increased GP access, increased in-patient stays, higher rates of joint replacement surgery, and the increased cost of caring for non-articular co-morbidity such as steroid-induced adverse events (osteoporosis, diabetes, cardiovascular disease. Although robust broad data on reduced health care utilization in RA is lacking, there is data that demonstrates reduced orthopaedic interventions since the advent of the widespread use ofhe bDMARDs. For example, new onset of rheumatoid cervical spine disease (atlanto-axial subluxation) has been shown to be reduced in patients receiving bDMARDs (*Kaito et al. Spine 2103; 38 (26): 2258-63*), a complication that has a significant impact on the patient and the NHS. Similarly, rates of hand surgery in RA patients have also declined, utilising data from the ERAS and ERAN cohorts. This decline has again occurred during the era of widespread use of bDMARDs (*Nikiphorou et al. Arthritis Rhematol 2014; 66 (5): 1081-9*). Finally,

the historical complications of poorly controlled RA (rheumatoid vasculitis, skin ulcers, and ophthalmic complications) are now rarely seen in modern clinical practice and the cost to the patient and NHS of such devastating manifestations is not captured by the AG report.

Estimation of HAQ progression on cDMARD

We note the conclusions of the assessment group that HAQ progression on cDMARDs is unlikely to be linear over time and that the lowest ICERs derived from the recent analysis are £42,300 to £44,700 for the most severe patients with the greatest HAQ progression who have had methotrexate, and £47,800 to £54,600 for moderately severe patients. We note that these data have been described in the report by the DSU in February 2015 on *'Progression of Disease in People with rheumatoid Arthritis Treated with Non Biologic Therapies'*.

We consider that the increase in HAQ described in this document does not relate to the patients who would meet current NICE criteria for treatment with a biologic drug. Biologic drugs are only used in a minority of patients with RA. Approximately 10-15% of patients with RA fulfil the NICE criteria and are treated with biologic drugs. Only historical data sets that predate the availability of biologic drugs are appropriate to determine disease progression on conventional treatment: those eligible will have the benefit of treatment. If they are withdrawn from analysis the remaining cohort are not severe enough to warrant biologic treatment. In relation to the appropriate data sets, the Leiden data set largely predates the availability of infliximab but contains only 563 patients and therefore the 10-15% cohort of patients who would fulfil NICE criteria would be too small for analysis. The BARFOT, NDB and ERAN datasets include follow up when biologic drugs were available.

The ERAS dataset benefits from being a cohort of UK patients and predates the availability of biologic drugs. The DSU evaluated 1430 patients in this dataset and found that 10% had failed two DMARDs and had a high DAS. We therefore consider this group to be the most appropriate to consider HAQ progression as a comparator with biologic therapy. The DSU found that the mean annual increase in HAQ in ERAS after the first two years was 0.0542 (table 7). In our opinion, the lower annual increase in HAQ in the other datasets (ERAN, Leiden, BARFOT, NDB) is a result of either these patients being treated with biologic drugs or a channelling bias in the remaining patients. We also note the DSU have calculated that the increase in HAQ reduces over time. However, Figure 7 indicates the reduction in the number of patients observed over time and reflects the degree of uncertainty in projected HAQ progression beyond 5 years.

In view of the importance of this comparator data we have commissioned an independent assessment of HAQ progression in the ERAS database in patients who would fulfil current NICE criteria for a biologic drug (appendix). This assessment found a rate of 0.05741 or 0.065531 depending on the regression model, similar to that expressed by the DSU in table 7. We therefore conclude that using the most appropriate data, HAQ progression in patients eligible for biologic therapy is approximately 0.06 p.a. This figure is the same as the estimated figure used in TA130.

Derivation of health utility scores from HAQ score

Estimating cost effectiveness of therapies requires the use of health utility scores, such as EQ-5D. HAQ score is routinely collected in clinical trials of biologics in RA whereas EQ-5D is not. NICE Methods guide suggest that mapping from alternative clinical outcomes is an acceptable method for estimating EQ-5D in the absence of direct evidence. Harrison and colleagues (*Harrison et al.Health and Quality of Life Outcomes 2010, 8:21*) describe EQ-5D data derived from HAQ RA is relatively accurate in stable, established cohorts but less accurate in patients with early, active disease, and that the difference between estimated and measured EQ5D was clinically important. The variance in derived utility scores was also higher than in measured scores. The underestimation of change in utility scores over time

was most marked in those with early, active disease, the population of current patients most likely to receive to receive bDMARDs.

This may lead to conservative estimates of cost effectiveness and an underestimation of QALYs, thereby increasing the likelihood of truly cost effective treatments being rejected if mapped utility values are used. We therefore caution against relying solely on a method of estimating health utility from HAQ that introduces further variation into the assessment process, especially given the observation that poorer performance of predicted utility values in patients with more active disease, where pain and fatigue may play a greater role, counsels against mapping utility scores for measures of functional disability alone in this context.

Discount rates and the changing financial environment of biologic therapies in the UK

We are concerned that the negative effect on ICERs from the change in discount rates from previous MTAs, without a concomitant change in the ICER threshold, indicates that biologic treatment is no longer cost effective. This is despite the lack of any data to indicate that TNFi are less effective than previous MTAs. Previous NICE guidelines on economic evaluation were the first national guidelines to prescribe such differential discounting (6% for costs and 1.5% for effects). However, setting rates for cost and benefits at 3.5% implies a lower weight for future effects. We agree with WBF Brouwer and colleagues who have argued that this change is not based on contemporary health economic literature nor convincingly justified (*BMJ. 2005 Aug 20; 331(7514): 446–448*). We also note that the *Guide to the methods of technology appraisal 2013* states:

6.2.19 In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.

We consider that this applies to the benefits of biologic therapies in RA and health benefits should be discounted at a lower rate. PPRS 2014 ensures that this would not submit the NHS to irrecoverable costs. We conclude that it is inappropriate to change the discount for health benefits from TA130. However, we consider that with the introduction of biosimilar bDMARDs it is appropriate to consider an increased discount rate for costs. We would like to highlight that the financial environment of biological therapies in RA is changing, and will continue to do so for the foreseeable future. Biosimilar infliximab has recently received marketing authorisation in the UK and is offered to NHS Trusts at a substantially reduced cost compared to parent drug (Remicade). Further biosimilars are likely to receive marketing authorisation in 2015/16, potentially disrupting the biologics financial environment even further. The assessment of cost-effectiveness of bDMARDs is therefore likely to change substantially in the near future.

Fairness

We agree with the DSU regarding the importance of HAQ progression in patients with severe RA not treated with biologic therapy. As discussed above, we conclude that HAQ progression of approximately 0.06 is an accurate reflection of the appropriate data. We also conclude that applying new discount rates that fail to reflect the major benefit of treatment from biologic treatment are inappropriate. We consider that it is inappropriate to change the parameters used by NICE in previous

MTAs. This has the effect of 'changing the goalposts' compared with TA130 and if this is accepted by the appraisal committee we consider this would not meet NICE's standards of fairness.

We agree with the AGs conclusions on p 487 (ScHARR Updated assessment report) that *"These estimates are considerably lower if a different assumption, used in previous NICE appraisals were adopted"* and therefore consider that in view of the evaluation of HAQ progression from ERAS and the discussion of discount rates, the most appropriate ICERs are those in table 171 (p 397) using linear HAQ progression and previous discount rates. The ICER of £22,300 for severe RA is well below NICEs threshold of £30.000 for innovative technologies and we would hope the committee will acknowledge that bDMARDs are cost effective for severe RA.

We are not aware of any new data since TA130 that would indicate bDMARDs are less effective in severe RA and consider that it would not meet NICE's standards of either reasonableness or fairness to conclude that all the previous NICE appraisals in recommending biologic treatment were incorrect.

Moderate disease and stopping rules

Previous TAs for bDMARDs have not accepted moderate disease (DAS score of 3.2 to 5.1) as an indication for therapy. However, patients with moderate disease who have failed cDMARDs have significant pain and disability. Most European countries do not preclude bDMARDs from these patients and the current evidence indicates that bDMARDs are also cost effective in these patients. We note the AGs conclusions that ICERs are only marginally higher for moderate disease (p 486 *"These values are marginally higher for moderate RA patients"*) and consider that the ScHARR Health economic analysis supports the use of biologic therapy in moderate RA in addition to severe disease. The most appropriate ICERs are those in table 171 (p 397) using linear HAQ progression and previous discount rates. The ICER of £21,800 for moderate RA is also well below NICEs threshold for approving treatment. Although this would increase the number of patients treated, the PPRS 2014 agreement ensures this would not have a negative impact on NHS budgets.

We agree with the AGs comments regarding non-adherence to NICE guidance (p 487) and support cessation of any biologic drug in those who fail to have an adequate clinical response. We would urge the committee to emphasise this aspect in this appraisal.

Conclusions

Biologic DMARDs have changed the lives of patients with RA who have failed cDMARDs. We consider that the current evidence indicates that these compounds are cost effective in both severe and moderate RA. We consider that there are a number of assumptions in the current analysis that overestimate the costs of bDMARDs. We have shown that in patients who meet the current criteria for bDMARDs, the 0.06 p.a. rate of HAQ progression used in the health economic analysis for TA 130 is supported by the available data. We also consider that HAQ mapping to utility underestimates health improvement particularly in patients with early active disease. We consider that changing the discount rates from TA130 is inappropriate for these technologies and recognise that NICE methods allow the committee to address this. We consider that the DSU analysis have found that bDMARDs are cost effective for both severe and moderate disease and consider that NICE would not meet its own standards of reasonableness and fairness if it now concluded that bDMARDs for RA were not cost effective and that all previous TAs on bDMARDS were incorrect and their conclusions were false.

[redacted]

[redacted]

[redacted]

Appendix : Full details of ERAS data analysis

1. Analysis of severe subgroup – mixed effects regression model

Methodology

The dataset presented HAQ values of patients at 15 timepoints (year 1 to year 15). In order to analyse whether HAQ values changed over time and to calculate the rate of change a mixed-effects regression model was fitted to the data provided, including two random-effects for the intercept and slope for time. The model was developed with uncorrelated random effects. The change in HAQ was constrained to be linear over time. A fixed-effects term was included for DAS scores. Three dummy variables were incorporated for first DMARD, second DMARD and third DMARD. The model can be summarised as follows:

HAQ ~ 1 + time + DAS + DMARD1 + DMARD2 + DMARD3 + (1|subject) + (0+time|subject)

The analysis was conducted in R using the lmer function from the *lme4* package.

For the purposes of this analysis, the severe group of patients within the ERAS cohort was defined as those patients:

- with a DAS > 5.1 at all timepoints

AND

- who have received methotrexate *or* received at least two non-methotrexate DMARDs

Also, all patients with a HAQ score below 0.5 at any timepoint was excluded from the analysis. A total of 68 patients met this description.

For those patients who received a TNF inhibitor during the study, only data up the year prior to the receipt of the TNF inhibitor was included in the analysis.

Results and interpretation

- The average annual HAQ progression is determined as **0.065531** per year
- 95% confidence intervals for the average annual HAQ progression are: **[0.018, 0.119]**

Output from R

Full results of the regression analysis, as output by R, are as follows:

```
Linear mixed model fit by maximum likelihood  ['lmerMod']
Formula: haq ~ 1 + time + das + dm1 + dm2 + dm3 + (1 | id) + (0 + time |      id)
   Data: set

    AIC      BIC   logLik deviance df.resid
   120.1    142.4    -51.0    102.1       79
Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.57547 -0.48767  0.04516  0.41962  2.52762
Random effects:
 Groups   Name        Variance Std.Dev.
 id       (Intercept) 0.231286 0.48092
 id.1     time        0.003113 0.05579
 Residual             0.078225 0.27969
Number of obs: 88, groups:  id, 32
Fixed effects:
```

```
            Estimate Std. Error t value
(Intercept)  1.055605   0.350146   3.015
time         0.065531   0.023486   2.790
das          0.131441   0.048114   2.732
dm1          0.004520   0.020835   0.217
dm2         -0.007728   0.020321  -0.380
dm3          0.002806   0.003335   0.841

Correlation of Fixed Effects:
    (Intr) time   das    dm1    dm2
time -0.195
das  -0.931  0.055
dm1   0.096  0.005 -0.034
dm2  -0.142 -0.010  0.068 -0.964
dm3  -0.104  0.033 -0.042 -0.320  0.194
```

And the calculation of the confidence intervals yields the following results:

```
> confint(fit,level=0.95)
Computing profile confidence intervals ...
                 2.5 %      97.5 %
.sig01       0.338243317 0.676621535
.sig02       0.000000000 0.108217885
.sigma       0.222783116 0.361291295
(Intercept)  0.345163491 1.760367676
time         0.017982974 0.118778073
das          0.033810589 0.231395915
dm1         -0.037731939 0.047547180
dm2         -0.049931463 0.033472207
dm3         -0.003930746 0.009620355
```

2. Analysis of severe subgroup – linear regression model

Methodology

The dataset presented HAQ values of patients at 17 timepoints: baseline (year 0), 6 months (year 0.5), and yearly data from year 1 to year 15 (compared to the above analysis, HAQ data at the year 0 timepoint and the 6 month timepoint were not excluded). In order to analyse whether HAQ values changed over time and to calculate the rate of change a linear regression model was fitted to the data provided. HAQ was considered the dependent variable and time the only independent or explanatory variable, as per the equation below:

$$HAQ \sim time$$

The analysis was conducted in R using the lm function from the *stats* package.

For the purposes of this analysis, the severe group of patients within the ERAS cohort was defined as those patients:

- with a DAS > 5.1 at all timepoints

AND

- who have received methotrexate *or* received at least two non-methotrexate DMARDs

A total of 84 patients met this description.

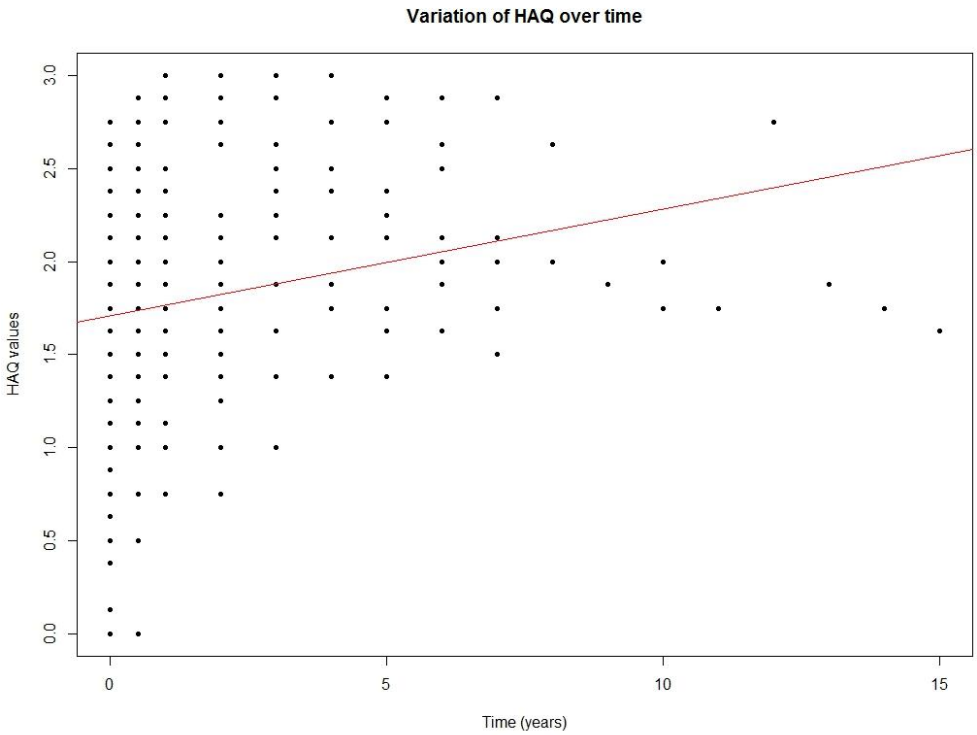
For those patients who received a TNF inhibitor during the study, only data up the year prior to the receipt of the TNF inhibitor was included in the analysis.

Results

- HAQ values were seen to change significantly over time
- The linear model fitted is as follows:

$$HAQ = 1.75038 + 0.05742 * time \text{ (in years)}$$

- The average annual HAQ progression is therefore determined as **0.05741** per year; by way of comparison, the results of the same analysis conducted in the entire ERAS cohort (ie. not the severe population only) found HAQ progression in this broader population to be **0.012709** (results not shown)
- 95% confidence intervals for the average annual HAQ progression are: [0.028, 0.087]
- A graphical representation of the results is provided below:



Output from R

Full results of the analysis, as output by R, are as follows:

```
Call:
lm(formula = results$HAQ ~ results$Time)
Residuals:
    Min      1Q   Median      3Q     Max
-1.73909 -0.42489  0.00414  0.42858  1.23220
Coefficients:
            Estimate Std. Error t value            Pr(>|t|)
(Intercept)   1.71038    0.04859  35.202 < 0.0000000000000002 ***
results$Time  0.05742    0.01503   3.819            0.000169 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Residual standard error: 0.6345 on 250 degrees of freedom
  (1176 observations deleted due to missingness)
Multiple R-squared:  0.05513,  Adjusted R-squared:  0.05135
F-statistic: 14.59 on 1 and 250 DF,  p-value: 0.0001689
> confint(fit,"(Intercept)",level=0.95)
             2.5 %   97.5 %
(Intercept) 1.614686 1.806071
> confint(fit,"results$Time",level=0.95)
                2.5 %   97.5 %
results$Time 0.02780848 0.087028
```