Ms Lori Farrer
Programme Manager
NICE
Level 1a, City Tower
Piccadilly Plaza
Manchester M1 4BT
(sent by email to TACommC@nice.org.uk)

24 September 2013

Dear Ms Farrer,

British Society for Rheumatology Response to Assessment Report on Multiple Technology Appraisal ID537 (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis

A combined response from [redacted] and [redacted]

We are grateful for the opportunity of responding to the assessment report on the MTA. We welcome the conclusions that the cost effectiveness of treating moderate disease is similar to severe disease. However, we have serious concerns regarding the conclusions based on the ICERs for biological treatment in this assessment, which are far greater than other health economic evaluations undertaken for biologic treatment of rheumatoid arthritis in TA130, TA186, TA225, TA247 and TA280. The conclusions in this report raise doubt regarding the cost effectiveness of all treatment. Independent economic assessments in each guidance concluded that all the drugs being evaluated in ID537 were a cost effective use of NHS resources. In addition we note that an earlier evaluation by the Sheffield unit of infliximab, etanercept and adalimumab from the BSRBR also found these drugs to be cost effective. *"The basecase cost per quality adjusted life-year gained by using TNF-_ antagonist therapies is estimated at £23 882, with probabilistic uncertainty analysis suggesting that the probability that treatments are below £30 000 per QALY is around 84%."* [(1)]

The management of RA has been revolutionised by the introduction of biologic treatments. They are the only evidence-based effective therapeutic approach for patients with severe active disease that fail to respond to conventional DMARDs such as methotrexate. It is inconceivable that patients with RA in England would not have access to these treatments if and when they need them. The existing NICE HTA guidance for funding biologics in rheumatoid arthritis require patients to have substantially more active and prolonged disease than is required by their European licensed indications. These excess levels of severity are also higher than those in all the clinical trials on which the evidence base for efficacy exists. Any further restrictions on access to highly effective biological treatments can only move NICE HTA Guidance away from the existing evidence base. This would potentially undermine the credibility of the process. There is substantial clinical evidence that the outcome of rheumatoid arthritis is substantially worse in England compared to many areas of continental Western Europe, such as the Netherlands. This disparity is shown in international surveys such as QUEST-RA[(2).] Part of the explanation for such disparities is likely to be the substantially higher hurdle for initiating biologic treatments within England compared to continental European countries[(3)]. Further non-evidence based restrictions to accessing highly effective biologic treatments is likely to substantially worsen results in England compared to these comparator countries.

We have comments under 5 headings:

1. HAQ progression
2. Disease duration
3. Eligibility criteria
4. Taking non-responders off biologics
5. Other considerations

1. HAQ progression

We agree with the authors concerns regarding *"the sensitivity of cost-effectiveness models to key parameters and modelling assumptions"* (p186). The various economic models which have been produced to guide treatment decisions about access to biologics in RA include a large number of unproven assumptions. These assumptions are most marked with regard to HAQ progression. Using data from observational cohorts which have followed all patients presenting to specialist units over time is clearly inappropriate as most of these patients will have mild disease and would never have required biologic treatments. It is therefore inevitable these approaches will find the progression of HAQ is only modest. The work referenced as numbers as 270 and 271 in the document show that rheumatoid arthritis is a very heterogeneous disease, with four distinct HAQ progressions using latent class growth models on analysing two independent observational datasets. Only patients with highly active and rapidly disabling disease failing on cDMARDs would be considered for biological therapy, and the HAQ progression in these patients will be very different from those with milder disease who will never be considered for bDMARDs. In both cohorts there were demographic and disease characteristics that could be used to predict membership of classes with worse HAQ progression. If the HAQ progression for cDMARDs was confined to those patients most likely to need bDMARDs, this would be more appropriate than amalgamating all RA patients.

However, the ScHARR analysis has used data from the whole ERAS cohort to determine the expected progression and concluded that the rate of progression on cDMARDs is less than has been accepted in previous appraisals. We agree with the authors of the Assessment Report at the foot of page 456 where they state that HAQ *"progression calculated from ERAS data…… may underestimate HAQ progression as it may contain patients who would not receive bDMARDs."* We also agree with the clinical advisors in the assessment group when they cautioned that the database that has been used includes a spectrum of patients that have milder disease and would not receive biologic drugs.(p373). The same criticism relates to the studies in table 191. We therefore consider that using the ERAS data for determining HAQ progression on cDMARDs is inappropriate when used as a comparator to biologic drugs. The only appropriate available data, noted in the SCHARR report but not used for modelling, suggests that in severe RA in England and Wales the progression of HAQ in the absence of biologics is very high indeed. Further restricting access to highly effective biological treatments on the basis of these economic models is, in our view, inappropriate and would not be based on reasonable comparisons.

2. Disease duration

The authors of the ScHARR report have clearly recognised that the ERAS HAQ progression may not be acceptable as they have also modelled cost-effectiveness with linear progression of HAQ on cDMARDs, as used in previous NICE appraisals. We note that when using linear HAQ data and discounting of 6% p.a. for costs and 1.5% p.a. for QALYs, the ICER values are similar to those in the Brennan study and within the values accepted as cost effective by NICE. However, when discounting at 3.5% p.a. as recommended in the current NICE methods guide for technology appraisals, the ICER values are between £30-35,000. We consider that even if NICE were to

apply this revised discount rate there remains an underestimate of cost effectiveness because of the data that have been used to drive the model.

It was noted in TA130 that cost effectiveness was greater in patients with early rather than late disease, a point also raised in the ScHARR report: the authors quote Hernandes' opinion (p380) that the ICER may be affected by 20% depending on the severity of the patients. One explanation for this is that many patients with late disease have a greater irreversible component of HAQ than those with shorter disease duration. We would like to emphasise that the majority of patients in the BSRBR have a longer duration of disease than in the clinical trials and in clinical practice; most patients who are currently treated with their first biologic drug will have a significantly shorter duration of disease than in the BSRBR. Patients recruited into the BSRBR have established severe disease with disease duration of around 13 years (see table 189 page 367). Therefore using data from these patients will create an erroneously high ICER.

We also note that the relationship between HAQ and EQ-5D that drives the cost benefit analysis has been derived from a US cohort of patients. We consider that the inherent assumption that these populations are similar is mistaken. US populations and the population in the BSRBR – especially those entered when the register was first established – are almost certainly different in the severity, duration and availability of treatment and may also lead to an increase in the ICER.

3. Eligibility criteria

We fully appreciate the challenges in using high cost biologic treatments and have no wish to extend their use unreasonably or without clinical evidence. The current criteria for access in the UK have several limitations. However, they have stood the test of time well and major changes in them do not seem warranted. The argument that most patients with active RA should try intensive DMARDs prior to starting biologics is reasonable and well argued. There would be good reasons to make the case for requiring intensive DMARDs to be used (ie patients must receive at least 6 months intensive DMARD treatment prior to starting biologics). The exact definition of intensive DMARD treatment would require substantial expert review as the evidence base in relatively controversial about which approaches are best and which have significant problems (for example high dose steroids may have unacceptable risks for many patients).

We agree with the assessment group that it is inappropriate to use bDMARDs as first line drugs with the TEAR and SWEFOT studies suggest making best use of combinations of conventional DMARDs being almost equivalent to, but substantially cheaper than first line or early introduction of biologics[4,5]. We have argued in previous submissions that the cost effectiveness of bDMARDs would increase if clinical colleagues were obliged to make best use of cDMARDs in keeping with NICE guideline CG79. This would also decrease the need to use biologics. Trials of intensive conventional therapy from the start of disease have been shown to potentially halve the need to use biologics. One example is the recently reported tREACH trial. Combination therapies (methotrexate, sulfasalazine and hydroxychloroquine) were better than methotrexate monotherapy, and led to a 50% decrease in the need to use biological therapies. Bridging therapies with oral or intramuscular steroids showed no differences between these strategies (6). The UK TEAR study found the outcome of combination therapy was similar whether the drugs were initiated together or added sequentially for persistent disease (7) – the importance is to monitor regularly and treat aggressively until in remission.

In our Joint Statement on the scope we suggested the following be adopted as an eligibility criterion:

"Patients should have undergone trials of at least two DMARDs used in combination, including methotrexate orally or subcutaneously (unless contraindicated), as well as a treatment with oral or

intramuscular steroids, with two months at standard doses, unless significant toxicity has limited the dose or duration of treatment of the DMARDs".

A Best Practice Tariff commenced in April 2013 to financially incentivise hospitals to see patients with early inflammatory arthritis (EIA) within 3 weeks of referral, and start DMARDs where appropriate within a further 3 weeks, then follow patients up regularly to measure and decrease their disease activity[8]. A national HQIP audit on EIA and RA will start early in 2014, with measures of delays in getting patients onto DMARDs, and benchmarking between units to improve services[9]. It is hoped that these initiatives will incentivise English rheumatologists to make best use of cDMARDs and see patients quickly and treat them intensively. We feel that if the Assessment Report had been able to confine itself to studies where best and evidence based use had been made of cDMARDs prior to bDMARDs, this would have improved the cost effectiveness of the latter.

We are pleased to see that the ICERs for moderate and severe RA were broadly similar. We appreciate that if the eligibility for access to first bDMARD was decreased to a DAS28 of 3.2 this may increase the number of patients eligible to go onto biologics (although we would hope that much of this could be tempered by making better use of cDMARDs, as stated above). NICE RA management guidelines advocate the use of combinations of DMARDs and short term steroids in active RA[10]. One sign that the DMARDs are working is if the steroids can be gradually withdrawn. Some patients may have a DAS28 between 3.2 and 5.1, but if their steroids were withdrawn this would lead to a DAS28 > 5.1. It would be inhumane in clinical practice to have to decrease or withdraw steroids in order for patients to fulfil the criteria to commence their first biologic. CG79 states that long term steroids should be avoided wherever possible, using biologics where necessary in order to achieve this[10]. Patients with a DAS28 > 3.2 in spite of intensive DMARDs should have access to biologics, particularly if they are steroid dependent. We would like to draw the Assessment Group and Committee's attention to this common clinical problem, and hope this will lead to a change in eligibility criteria, particularly as the cost effectiveness of using these drugs is little different in moderate and severe RA.

Most studies covered by the Assessment Group were on patients identified at a single time point to have active disease. Measuring disease activity on two occasions a month apart painfully delays the inevitable need for biologics in 97.2% of patients[11]. Patients with psoriatic arthritis only require a single assessment of disease activity, putting RA patients at an unfair disadvantage[12]. RA patients should have a single assessment of disease activity having failed to respond to two DMARDs.

4. Taking non-responders off biologics

We also consider it crucial to ensure patients who do not respond to biologics have these high-cost treatments changed at the earliest opportunity. There are mentions in the Assessment Group's report of how keeping non-responders on biologics renders them much less cost effective, and BSRBR data demonstrates that this happens. We would like to point out that much of this data is historic, and collected at a time when anti-TNF drugs were the only available biological drugs with no other choice if the patient failed on this drug. Now that other choices have been made available it is likely that deviation away from NICE guidelines will have decreased. It is incumbent on clinicians to demonstrate to commissioners that the guidelines are followed. At BSR we are aware of centres that work closely with commissioners to show that well funded biologics services that follow patients up and monitor their response to treatment, and stop ineffective drugs where appropriate, can be highly cost effective, and we would encourage this practice. We have suggested to NHS England that a Best Practice Tariff should be implemented for compliance with NICE guidelines on biologics in order to incentivise all units to follow this.

5. Other considerations

We also note that the Assessment group mention that lost productivity has not been included in the model and this would favour bDMARDs. This relates not only to the patient but to the family and carers who may have to give up productive employment to care for their relative or partner. This was illustrated in a study of patients with early RA prior to the introduction of biologic dugs (12). RA had an impact on one of the socio-economic items measured in almost all patients, and was a major impact in 58%. Work disability was 4-15 times higher than in the general population. After 3 years, 42% of the patients were registered as work disabled. We understand that there is a commitment by NICE to consider full socio-economic effects of a disease as part of Value Based Pricing, and hope that these factors can also be taken into account in the analysis, or at the very least consideration of these factors be included in the interpretation of the results.

Signed: [redacted] [redacted]

References

1. Brennan A et al Rheumatology 2007;46:1345–1354.
2. Sokka T, Kautiainen H, Pincus T, et al. Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST–RA database *Ann Rheum Dis* 2009;68:1666-1672
3. Hockley T, Costa-Font JA. Common Disease with Uncommon Treatment. European Guideline Variations and Access to Innovative Therapies for Rheumatoid Arthritis. Published by LSE; June 2012. http://www.policy-centre.com/downloads/Guideline-Variations-Report-2012-Final.pdf
4. Moreland LW, O'Dell JR, Paulus HE et al. A randomised comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis. Arthritis Rheum 2012:64:2824-35
5. van Vollenhoven RF, Geborek P, Forslind K et al. Conventional combination therapy versus biological treatment in methotrexate refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712-8
6. de Jong PH, Hazes JM, Barendregt PJ et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: results of the tREACH trial. Ann Rheum Dis 2013;72:72-8.
7. Porter D. Intensive management of early rheumatoid arthritis: the TICORA and TEAR studies Clin Exp Rheumatol 2012; 30 (Suppl. 73):S32-S34
8. http://www.rheumatology.org.uk/resources/best_practice_tariff/default.aspx
9. http://www.hqip.org.uk/new-national-clinical-audits-for-kidney-disease-and-arthritis/
10. http://www.nice.org.uk/nicemedia/pdf/CG79NICEGuideline.pdf
11. Smith N, Gadsby K, Butt S et al. Is pre-assessment for anti-TNF therapy necessary in the UK? Analysis of DAS28 in six centres. Rheumatology 2007;46:1557-9.
12. http://publications.nice.org.uk/etanercept-infliximab-and-adalimumab-for-the-treatment-of-psoriatic-arthritis-ta199

12. Albers JMC, Kuper HH, van Riel PLCM, et al. Socio-economic consequences of rheumatoid arthritis in the first years of disease. Rheumatology 1999; **38**: 423-430.