The British Society for Rheumatology

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Dear Dr Longson

**Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)**

The British Society for Rheumatology (BSR) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. The comments have been prepared by [redacted] and [redacted]

We also support the submissions made by NRAS and Arthritis Care.

## 1. Over-estimation of Response to DMARDs after TNF failure

In 4.3.10 the committee concluded; *"That, on the basis of clinical opinion, the effect of conventional DMARDs in people for whom a TNF inhibitor had failed was likely to be small, but the relative effect in comparison with biological treatments was not currently quantifiable".*

In the Addendum Report, from the West Midlands Health Technology Assessment Collaboration the assessment group concluded on p77 that; "*the results were fairly sensitive to the assumptions on efficacy of conventional DMARDs given after biologic therapy. The differences between the reference case results in the BRAM and those produced by Abbott and Schering-Plough can be explained by changing a small number of parameters in the model."*

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We broadly agree with these conclusions. As we discussed at the Appraisal Committee meeting, we would particularly support the poor late DMARDs scenario, as there is evidence to support poor benefits from conventional DMARDs after the failure of anti-TNF. Analysis of the BeSt trial suggested that if patients fail on methotrexate in any of the conventional treatment arms, there is only a 15% chance that they will respond to subsequent conventional DMARDs (van der Kooij SM et al. Ann Rheum Dis 2007;66:1356-62). Furthermore, this was in patients not exposed to anti-TNF, which would suggest that in patients failing on anti-TNF, the success rate on subsequent DMARDs would be even lower. We wish to emphasise that the expected response in patients with established RA is anticipated to be even worse than that seen in the BeSt study. We feel that an estimate of 0% improvement on conventional DMARDs after the failure of anti-TNF is likely to be much closer to reality than the 50% improvement quoted in previous BRAM models. Table 21 on page 76 of the Addendum Report shows, under a variety of different scenarios, changing from adalimumab to infliximab achieves ICERs close to £20,000. We would suggest that Table 21 supports the cost effectiveness of infliximab following the failure of adalimumab, and that this should be an alternative strategy to rituximab. We would like to seek clarification on why other approaches such as IFX-ETN and IFX-ADA are not included in the Table?

We therefore broadly agree with the committee's conclusions in 4.3.16; *"that the Assessment Group may have overestimated the efficacy of conventional DMARDs",* and urge the committee to consider the ICERs described in the addendum report by the assessment group.

### *2.* Inappropriate use of HAQ multiplier

We would also wish to agree with the conclusion in 4.3.15; "t*he Committee concluded that patients may derive benefits from the treatment that are not reflected in HAQ score because of irreversible joint damage".*

However, we wish to express concern that this has not been taken into account in the assessment report. Aletaha et al (Arthritis & Rheum 2006; 54: 2784-2792) were able to quantify the reduced response of the HAQ to treatment in established disease. They found that among the 295 patients in whom clinical remission was achieved, the average HAQ scores despite clinical remission increased progressively with the duration of RA, from 0.19 (<2 years of RA) to 0.36 (2-<5 years) to 0.38 (5-<10 years) to 0.55 (≥10 years) ($P$ < 0.001). In addition they found that the reversibility of HAQ scores decreased with the duration of RA (median 100%, 83.3%, 81.9%, and 66.7%, respectively; $P$ < 0.001). We consider that these observations should have been taken into account with the assessment group modelling and would identify a greater improvement in utility from treatment.

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We also consider that this data suggests the use of the HAQ multiplier to be inappropriate. The Committee considered in 4.3.16; "*that the use of such a multiplier to model changes in HAQ meant that absolute changes in the upper range of the HAQ scores were larger than those in the lower range, and that therefore people with more severe disease would have larger HAQ improvements than if the HAQ scores from the clinical studies were used directly. Bearing in mind these considerations, the Committee accepted the use of a HAQ multiplier as a reasonable way to model changes in HAQ score".*

This approach would be relevant in patients without irreversible disability but is likely to underestimate the benefits of treatment in patients with late disease who have established joint damage and would hope the assessment group would be able to model the health economic analysis to take these data into account.

### 3. Failure to incorporate stopping rules in the economic model

We are concerned that the health economic analysis by the assessment group does not take into account stopping rules as expressed in the NICE guidance and BSR guidelines. In 4.3.20 it is stated that; "*the Committee heard from the clinical specialists that data from the British Society for Rheumatology Biologics Register indicate that a number of people will continue treatment with a TNF inhibitor even in the absence of such a response, indicating that the use of stopping rules does not reflect current clinical practice. It further heard from the Assessment Group that for this reason stopping rules based on a response criterion had not been incorporated into the Birmingham Rheumatoid Arthritis Model base-case analysis. The Committee understood that the Birmingham Rheumatoid Arthritis Model was not designed in a way which could incorporate stopping rules based on a response criterion. The Committee noted, however, that a scenario analysis which included the proportions of people stopping treatment early that were used in the manufacturers' response-based models lowered the ICERs for the TNF inhibitors and abatacept by approximately £10,000 per QALY gained. The Committee did not consider that the Assessment Group's analysis could be used as a basis for decision making because it did not fully incorporate response criteria. In addition, the Committee questioned if the application of such response criteria would be reflective of clinical practice".*

It is our view that health economic evaluation must include stopping rules as this is adopted by responsible prescribers and that NICE guidance should be based on best treatment and clinical excellence and not a pragmatic approach by some rheumatologists. In addition we are aware that health commissioners are increasingly likely to 'police' the stopping rules of patients. We consider that it is inappropriate not to incorporate stopping rules in the analysis while issuing guidance that patients should stop treatment if there is inadequate response.

## Conclusion

We are grateful to the assessment group for undertaking additional analysis that indicates the reduction in ICERs when modelling for a poor response from DMARDs after TNF failure. We consider these results to be closer to real life experience. In addition we consider that if the response to HAQ in point 2 and the stopping rules in point 3 were included, the analysis would demonstrate all treatments to be cost effective after TNF failure. In addition the scope stated that certilizumab pegol would also be included as a comparator. Now that this has been accepted as cost-effective under a Patient Access Scheme, we would ask that this be included in analyses with the risk sharing strategy included in models.

Yours sincerely

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