[redacted]
National Institute for Health and Care Excellence
15th September, 2015

Dear [redacted]

Re: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

The National Rheumatoid Arthritis Society is grateful for the opportunity to review the Final Appraisal Determination (FAD) for the above appraisal. We have consulted with our Chief Medical Advisor and believe that we have grounds to appeal the FAD.

We welcome the committee's decision in relation to treatment of severe active rheumatoid arthritis, however we wish to appeal against the decision not to recommend treatment for certain patients with moderately active disease.

We wish to appeal on Ground 1a): that NICE has failed to act fairly, and also on Ground 2: that the recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal Points

We wish to appeal on two issues under Ground 1a and one issue under Ground 2.

Ground 1a) 1: In making the assessment that preceded the recommendation to only include those with severe disease, NICE has failed to act fairly

Both we and the BSR in our submissions following the meeting in February and when we attended the ACD meeting in May, provided substantial evidence to demonstrate that some patients with moderately active disease who fail to respond to combination therapy have a poor prognosis and just as poor outcomes as those with severe disease. Rheumatoid Arthritis, even in patients with moderate disease, is far from being a benign disease and the reality for patients with inadequately controlled disease is increased morbidity and mortality. The morbidity of moderately active disease includes fatigue, pain, depression, and work disability, all of which have a substantially detrimental economic impact for the NHS and wider economy. People tend to think that 'you don't die from RA' but in fact you can die early and this is frequently overlooked we believe.[1] The data presented by BSR in their submission and in their Appeal is in keeping with published evidence and the reported experience of people we support, that the largest degree of damage occurs in patients with persistently moderate disease activity.

We were presented with new information from the DSU which was circulated shortly prior to the Appraisal meeting on 21st May which included revised ICERs, the DSU having found errors in the previous health economic analysis. These revised ICERs were clearly within the £20-£30K threshold for ***both*** the severe and the moderate disease groups. These new data produced by NICE therefore supported the cost effectiveness argument for treatment to be available for both groups.

The Guide to the Processes of Technology Appraisal 2014 states at 3.7.3 that the committee papers consist of "comments from consultees and commentators on the assessment report". The BSR have argued that they were denied the opportunity of providing a written explanation of how these groups could be defined prior to the meeting on 21st May. The BSR discussed the proposals regarding the parameters for moderate patients with us prior to their submission following the ACD and we agreed with them but we did not feel that a patient group was in a position to make a scientific argument about these parameters. However, knowing that the BSR had made a robust argument for treating moderate disease we supported their response to the ACD and in tandem with them do not now have an opportunity to respond to the FAD about the proposals.

Patients are assessed with regard to the likelihood of structural damage progression and concommitant functional loss on the basis of ACPA and RF positivity, as well as having regular monitoring of CRP levels in routine clinical practice and we could have provided supporting information to confirm this from a patient perspective had we been given the opportunity. These markers are strong predictors of progressive disease[2] as evidenced in the BSR submission after the Appraisal meeting on 21st May. Our submission for the Appraisal meeting in May provided significant evidence of the impact on individuals' lives where people on standard DMARDs (not meeting the eligibility criteria for biologic DMARDS) were inadequately controlled and quality of life was poor with ability to work much reduced. Inability to work has a further major impact on mental health beyond that of the pain and lack of function as demonstrated in our previous submission.

Therefore we believe that not having the opportunity to respond to the Assessment Group data as detailed above was procedurally unfair.

Ground 1a) 2: In terms of due process, it was unfair for the committee to arrive at a decision apparently influenced by the views of one member who had not read all the relevant scientific evidence.

The very short time scales involved have proved unhelpful in providing appropriate written response to the new information following the ACD and, as it appeared from particular comments at the meeting, inadequate to ensure proper scrutiny of the submissions. In the Guide to the methods of technology appraisal 2013 it states in 6.2.5….."*This requires the Appraisal Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical specialists who have used the technology being appraised or are familiar with the relevant condition*". The Vice Chairman, [redacted], was critical of the BSR submission saying that it merely presented a hypothesis and not a true factual case, at the

same time admitting he had only read the titles of the referenced scientific papers (references *1-19 in the BSR Appeal*) not the contents. Another member made the point that increasing the number of patients eligible for biologic treatment would increase the NHS budget, which is not the case as the PPRS has capped NHS spend on drugs, but all the other committee members seemed to be accepting the arguments put forward. In fact, some committee members expressed concern that the proposals being put forward by the BSR were too rigorous and might deny treatment to some patients with moderate disease. The fact that not all the committee had had the opportunity to read all the relevant material before the meeting meant the decision was not fully informed by the evidence, and, it appears, may have been unduly influenced by a less informed member and we therefore agree with the BSR view that to dismiss their proposals which we fully supported, without the whole committee having read the relevant scientific papers that relate to this is unfair process.

Ground 2: It is unreasonable to conclude that treatment for moderately active RA is not cost effective when the ICERs presented were within the range defined by NICE as cost effective.

In the Guide to the methods of technology appraisal 2103 it states in 6.2.15…… "the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals". The pharmaceutical companies presented clearly evidenced ICERs for the treatment of moderate disease which ranged from £18,721 to £26,952. The ERG itself had evaluated the most costly ICER of the moderate group with the worst prognosis to be £28,500 (which reduced to £20,462 for the infliximab biosimilar). These ICERS are therefore all below the upper limit established by NICE to recommend treatment.

Following the ACD, the BSR had opportunity to explain to the committee in a written response how patients with the worst prognosis are defined in clinical practice. There is a substantial body of evidence to support the BSR's proposal to the committee indicating criteria that could be used to limit biologic DMARDs in moderate patients to those with the worst prognosis. The committee heard these criteria explained in detail and how they are used in day-to-day decision making as part of standard clinical practice. Several relevant references were cited including, for example, a study of 238 patients who were followed for 10 years where the authors concluded that *"Anti-CCP, IgM RF, ESR and female gender were independent predictors of radiographic progression and could be combined into an algorithm for better prediction. Patients with high levels of anti-CCP were especially prone to radiographic progression, indicating that the anti-CCP level may add prognostic information".*

We support the BSR and wish to respond to some specific statements in the FAD in order to underline the unreasonable (negative) recommendation for patients with moderate disease.

4.94 The Committee "*noted that no economic modelling had been provided for this group*" when in fact an ICER of £28,500 has been clearly shown for this group.

"… and that it had not been provided with any clinical evidence to support the assumption that disease with these characteristics would respond well to biological DMARDs."

En face, this is true but no opportunity has been provided to do so. In fact, most clinical trials have included patients with moderate disease with these criteria.

4.109: *"The Committee agreed that the biological DMARDs should be considered an innovative class of drugs. It also noted the comments from patient experts that biological DMARDs provide extensive benefits for people with rheumatoid arthritis and their families, in terms of both physical and mental health. It understood that the physical health benefits associated with biological DMARDs may encompass improvements in pain and cardiovascular health and well as benefits to the musculoskeletal system. On balance, based on the range of the most plausible ICERs, the Committee concluded that biological DMARDs in combination with methotrexate were a cost-effective use of NHS resources for people with severe active rheumatoid arthritis previously treated with methotrexate.'*

Just as there is a similar experience of the impact of RA across patients with severe disease and many of those with moderate disease, there is no difference between the benefits of treating severe and moderate disease.

In our survey which we presented in our response to the ACD we had many comments from people stuck on DMARDs with uncontrolled disease:

"I am hoping I will be able to have this to improve where I am now as I am on three DMARDs, steroids, naproxen and pain relief, so hoping there is something better to move onto as I feel awful on all the medication now"

"I would be devastated if I couldn't access biologics. I want to be able to continue to work. My RA is so debilitating at times that I physically can't get out of bed. Yet staying in bed hurts me so much. The only thing that helps at the moment is steroid injections."

In conclusion, despite substantial evidence being provided that many of these patients do not have benign disease; that biological DMARDS provide the same extensive benefits for patients with moderate disease; that the ICERs lie within the threshold accepted by the committee; and that there is a robust method to identify patients with the worst prognosis who would benefit the most, the committee did not support treatment for this group. We consider this is unreasonable in light of the evidence and given the choice, we would prefer to have an oral hearing should the Appeal Committee agree to uphold this Appeal.

Chief Executive
National Rheumatoid Arthritis Society

NRAS Chief Medical Advisor
Norman Collisson Professor of Musculoskeletal Sciences, Kennedy Institute of Rheumatology
University of Oxford Botnar Research Centre

References

1 *Ann Rheum Dis* doi:10.1136/annrheumdis-2013-204021 - Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Joachim Listing et al

2 Syversen S et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis* 2008 67: 212–217