National Rheumatoid Arthritis Society

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Dear Jeremy

NRAS response to the Appraisal consultation document 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)

We are pleased to respond to the above ACD and also support submissions made by the BSR and RCN.

In response to the specific questions raised by NICE in the above ACD, we would respond as follows:

1. **Has all of the relevant evidence been taken into account?**

   We agree that relevant evidence has been taken into account, however, we have considerable and real concerns about the fact that the NICE Appraisal Committee (AC) have made an interim decision which has been based on:

   - In 4.2.27 Scenario analyses indicated that the results are subject to considerable uncertainty.
   - In 4.3.4 the AC acknowledged that the profile of current patients differs from that used in analysis of the BSRBR data.

- In 4.3.5 the AC acknowledge that it is inappropriate to assume a class effect for TNFs.

- In 4.3.6 the AC acknowledge the absence of rigorously controlled data on the clinical effectiveness of the sequential use of TNFs and in 4.3.14 agree that the evidence base available for sequential use does not currently allow for a robust analysis of the relative treatment effect.

- In 4.3.9 it was stated that there was insufficient evidence to make differential recommendations for sub-groups. We disagree with this and in fact, even Roche themselves are now recommending/marketing Rituximab for patients who are sero-positive because they acknowledge that treatments are more successful when they can be targeted in this way.

- In 4.3.10, we agree with the AC that that the effect of DMARDs post TNF failure is likely to be very small and certainly less than the 50% on which the economic modeling has been based.

- In 4.3.15 The AC accepts that HAQ does not incorporate some aspects of RA such as pain, fatigue and sleep disturbance all of which lead to a significant reduction in QoL and that patients may also derive benefits from treatment which are not reflected in HAQ. We have stated previously that we believe costs of the treatment of RA have been under-estimated (including cost of palliative care).

- Following on from the above point, we do not agree that it is 'reasonable' to assume that the shortcomings and inaccuracies in HAQ modeling (4.3.16) mean that this is a 'reasonable' way to model changes in HAQ score.

- The AC said that all models used included EQ5D data derived from HAQ and yet this was subject to considerable uncertainty.

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**

    - The AC have themselves pointed out and agreed that there are significant limitations in the robustness of data available.

- I do not believe that the totality of the patient pathway and the impact on individual lives has been sufficiently considered in this Appraisal. We should be including certolizumab pegol, abatacept and tocilizumab in the treatment pathway as this is what would happen in clinical practice if there were no restraints on use of biologic therapy. Certolizumab Pegol has been passed by NICE for use in the NHS, yet how will it be sequenced, given the complications outlined in the ACD?

- In paragraph 4.1.6 and 4.1.8 patients responded to Rituximab and abatacept equally in respect of ACR20 response and yet sero-negative sub group have no further treatment options should they fail TNF/Rituximab in spite of an effective treatment option with abatacept. We believe that under such circumstances abatacept is a viable option.

- From a patient and health professional perspective, the evidence that sequential use of TNF, particularly in secondary non-responders is effective for the majority of patients is clear and the AC have now acknowledged that all the TNFs work differently and it is therefore inappropriate to assume a 'class effect', (4.3.5). We would therefore argue that for secondary non-responders, a second TNF should be allowed, but agree that primary non-responders would be better at that stage to try a biologic with a different mechanism of action and this is supported by clause 4.1.9.

- We are extremely concerned about the resource impact and implications for the NHS in respect of patients who, having failed one TNF and RTX, are then expected to go back onto DMARDS which have already failed or are likely to have little or no effect, which leaves the option of long term use of steroids, something which the AC agree will increase possibility of recurrent infections and is not recommended in the NICE RA Guidelines. We have in our previous submission highlighted that the costs of palliative care, we believe, are significantly under-estimated by NICE and the burden that these patients will put on already stretched health professionals, particularly specialist nurses, is considerable. This can be very powerfully demonstrated by the story of one of our young volunteers, Justine, appended hereto.

- In previous submissions, I believe both we and the RCN have drawn attention to the huge number of beds which have now gone from rheumatology due to better and more effective treatment. This represents a major saving to the NHS yet I do not believe that these types of savings have ever been reflected in the

economic modeling. I am concerned that if we are not allowed effective use of a variety of biologic treatments in a patient's pathway that gradually we will start to see a pool of very ill patients (we are already seeing this reflected in calls to our helpline) who will require substantial resource and represent a high cost to the NHS. I think the point made in the RCN submission regarding psychological counseling for those not allowed to go onto another biologic option, when they are aware that there are effective drugs available elsewhere in the world, including Scotland (!), is a very valid one. Unfortunately we know how difficult it is to access such services in the NHS. This is reflected in the NAO report.

- We would appreciate understanding what access to research means in the context of this ACD and a second TNF. Does this include patients who may go onto the BSRBR? Given that the 3 TNF cohorts are now closed, we are concerned that whilst this may appear to be a research option, negotiation of additional TNF data collection for new patients as well as additional biologic agents is a very lengthy process for the BSR to arrange and we seek clarification on this matter.

3. Are the provisional recommendations of the AC sound and do they constitute a suitable basis for the preparation of guidance to the NHS?

- The cost to individuals, their families and carers and to the wider society of uncontrolled disease cannot be over-estimated. We shall be publishing a report on the 'Economic Burden of RA' at the end of March which will show that previous figures of total costs being in the £3 – 4 Billion, fall well short of the reality.

- We have just completed a survey of the impact of RA on individuals with RA across Scotland. This is a repeat of the work survey we undertook on a UK wide basis in 2007. The figures are very comparable, with 57% (nearly 30% in the UK wide survey) of people who have lost their job due to their RA, losing it within 1 year of diagnosis and 80% losing their job within 6 years of diagnosis (59% in respect of the UK wide survey). 80% of people in the recent Scotland survey said that fatigue was the biggest barrier to remain in work and yet this is not adequately reflected in HAQ. >65% said that pain was the biggest barrier to remaining in work and this, equally, is not adequately reflected in HAQ. It is no longer a supportable position to take for NICE to simply say that these costs are 'not within their remit'. NICE should be lobbying government to change their remit to reflect wider societal costs in their economic modeling. The figures in

the economic modeling contained in the NAO report and the work of Dame Carol Black support this.

- In the light of the above and the substantial lack of robust evidence which has informed the economic modeling on which the above ACD has made its interim recommendations, together with inadequate reflection of pain, fatigue and other symptoms which dramatically affect people's lives, would lead me to the obvious answer to this question – 'NO'!

4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

    - I believe that the clinical experts explained at some length in the meeting on 4th Feb. the heterogeneity of RA and we believe that whilst the matter of the sero-negative sub group has been discussed in the ACD, we believe that the conclusions drawn are totally discriminatory. Approximately 25-30% of the RA population are sero-negative and to deny them a second anti-TNF (secondary non-responders) or access to a biologic with a different mode of action (tocilizumab or abatacept) is an infringement of their human rights and, as far as dedicated rheumatology health professionals are concerned, unethical.

    - I believe that there is sufficient evidence to support use of a second TNF in secondary non-responders. Many people have successfully switched to a second TNF which has allowed them to enjoy a good quality of life and enabled them to remain working and contributing to their family and society. Primary non-responders are more likely to respond to a drug with a different mode of action and access only to Rituximab, whilst an effective option, is inadequate.

    - If we are not allowed to use the available biologic treatments, how are we to ever to reach the reality of 'personalised medicine'? In my last submission I highlighted the disconnect between the aims of the Office of Life Sciences and the restriction NICE is placing on best clinical practice and UK research and we are already seeing the impact of this in reduction of UK based clinical trials. Not being able to use clinically effective treatments like abatacept which is freely available elsewhere in Europe is damaging UK PLC.

The most valuable development in treating RA will be 'biomarkers' to help diagnose it early, identify those with more severe disease, and indicate the most appropriate therapy for each person. Biomarkers may even help to decide the best time to step down therapy. There is a huge amount of research taking place worldwide into RA, which reflects the excellent relationship between rheumatology health care professionals and people with RA. Patients are actively participating in research, to help scientists reach answers more quickly. The last thing we want is that this process is damaged in the UK because it is **only** by being able to target therapy in this way that this will, in time, change RA from a chronic, disabling disease to an acute condition that is potentially curable.

We would urge NICE to reconsider their interim guidance and allow greater flexibility in the sequencing of biologic therapies.

Yours sincerely

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Enc: Appendix 1