Technology Appraisals Project Manager
Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence (NICE) MidCity Place
71 High Holborn
London
WC1V 6NA

1st August, 2008

Dear

NRAS Appeal against Final Appraisal Document
Sequential use of Adalimumab, etanercept and Infliximab for the treatment of RA

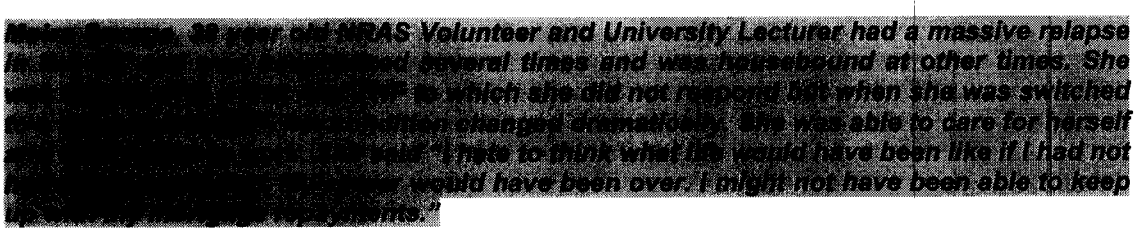
NRAS wish to appeal against the above Final Appraisal Document on sequential use of adalimumab, etanercept and infliximab for the treatment of Rheumatoid Arthritis. We also wish to support the ARMA Appeal and our name has been added to that also.

The implications for patients and clinicians of guidance in this FAD are hugely detrimental and very worrying. In the FAD (2.4) you state that the course of RA is heterogeneous and variable. This is indeed the case and treatment for patients with this life-long, painful and destructive disease must be viewed as a pathway of care and not as isolated and individual treatments which the MTA, HTA and STA process encourages. Diagnosed at a young age between the ages of 18 and 40, a person has many, many years to live with RA and given the individual way in which each person responds to the different treatments available and the fact that over time, the clinical effectiveness of a therapy can wane, it is not only essential, but vital that people have access to all drugs proven to be clinically effective when their disease is not responding and its destructive and disabling progress becomes uncontrolled.

I come to the core of our Appeal and confirm that we are appealing under Grounds Two (The Institute has prepared guidance which is perverse in the light of the evidence Submitted) and Three (The Institute has exceeded its powers).

1) Appealing under Ground Two: The Institute has prepared guidance which is perverse in the light of the evidence submitted.

Clinicians have no way of telling which patients might respond to a particular TNF antagonist. Thus it is entirely possible that they may decide to put a patient onto the drug which, for that individual, is going to be the least effective of the three options and reduces the opportunities for successful patient outcomes. The following case study is an example of this:



The FAD effectively denies *fair* access to the most suitable treatment because the first pick is a throw of the dice. This could lead to clinicians being open to threat of legal action by patients who will, understandably, feel let down if the first anti TNF is either ineffective or not effective enough. Switching patients to a second and even a third TNF *(my own personal circumstances are a classic case where the first TNF worked for about 3 years before gradually failing to control symptoms and disease progress, the second TNF did not work very well but the third TNF has been the most successful)* is considered current best practise in the UK, throughout Europe and the United States and has been for a number of years. Of note, for a sero-positive patient following the failure of a first anti-TNF, the chances of achieving a modest but clinically significant response at the ACR20 response level is essentially the same (at about 50%) whether the patient is switched to a second anti-TNF, rituximab or abatacept (which is not currently recommended for use by NICE on the grounds of unfavourable cost effectiveness). But it is not known at present to what degree of overlap there is in the proportion of patients responding to each of these 3 options (i.e. 2nd TNF, rituximab, or abatacept).

The data supporting widespread clinical use of anti-TNF switching continues to accumulate. For example, at the European League against Rheumatism meeting held in June this year in Paris, the following work was presented: Nalysnyk L, et al. *Treatment of Rheumatoid Arthritis After Failure of TNF Antagonists: A Systematic Review and Meta-Analysis.* EULAR; 2008. Abstract FRI0125. [Evidence Level B]. The findings are summarized below for the benefit of the committee.

Method: A systematic review of English literature published during 1/1995-11/2007 was performed and 2004-2007 EULAR and ACR meetings abstracts were also included. Interventional and observational studies were eligible and evaluated for quality. It identified 31 primary studies evaluating 5306 patients. The proportion of ACR and EULAR responders and the mean changes in DAS28 and HAQ were assessed. Meta-analytic pooling of outcomes across studies was performed using a restricted-maximum likelihood random-effects model. Efficacy was evaluated by type of failure, number of previous anti-TNFs failed, and stratified by study duration. Heterogeneity was examined using Cochrane's Q-statistic.

Summary of results tabulated below: This analysis confirms the effectiveness of switching in a proportion of patients having failed a first anti-TNF. Patients who switched due to primary failure with first anti-TNF agent have a lower response compared to those switching due to secondary or intolerance failure. Similarly, patients who failed two or more anti-TNF agents have lower responses compared to those who failed only one anti-TNF agent. As the data are consistent with widespread current best practise, in the UK and beyond, that when switching TNF inhibitors, therapies with different mode of action may need to be considered for patients failing their first anti-TNF.

% or Δ[95%CI]	Primary	Secondary	Overall Efficacy *	Intolerance	1 TNF Failed	≥2 TNF Failed
ACR20	47.8	62.2	58.5	66.3	62	43.4
ACR50	25.3	33.3	31.9	46.6	40.1	24
ACR70	9.7	13.4	12.7	28.9	20.2	10.8
EULAR (Good/ moderate)	65.5	72.5	69.9	71.5	66	71.3
DAS28	-1.5	-1.8	-1.6	-1.9	-1.5	-1.3
HAQ	-0.3	-0.4	-0.4	-0.3	-0.3	-0.3

*Primary, secondary and unspecified efficacy failure

The reality from a patient perspective is that switching to a second anti-TNF can be extremely beneficial, and certainly a preferable patient/clinician choice than to be put back onto DMARDs which have already failed and for which NICE acknowledge that any benefits are, at best, likely to be small and less clinically effective than an alternative TNF inhibitor (FAD section 4.3.7). Returning people to what can, at best be a regimen of drugs which will be unable to slow down the progress of their disease adequately and at worst be considered palliative care with large doses of steroids which carry unacceptable side effects and are not recommended by the BSR guidelines, is not offering patients 'quality' care and 'choice' which are at the heart of the Darzi Next Stage Review Final Report.

This decision also flies in the face of the recommendations in Dame Carol Black's recent report about supporting people to remain in work and the Department of Work and Pensions' aspirations to have 80% of working age population in work by 2010. Specifically it aims to 'move towards having 80 per cent of the working age population in employment', and 'to improve rights and opportunities for people with disabilities in a fair and inclusive society'. Access to the most effective treatments must go hand in hand with this legislation and not to acknowledge this is surely perverse. Indeed we remain concerned and unconvinced that the patient evidence has been considered in this FAD

and would ask for clarification of how the patient evidence has been considered in the decisions made?

It is very clear, not only to NRAS but also to other patients groups that the patient voice has minimal if any effect, because in reality the economic modelling only considers a minute number of factors that relate to the ***real*** costs of the patient with RA and other chronic diseases and I am not referring to work related disability here, which we are well aware is outside the current remit of NICE. In my experience the Review Panel are fundamentally not interested in patient quality of life issues and their primary focus is all about cost.

This NICE decision also denies patients clinically effective drugs, readily available to people with RA across Europe (and the USA), which is a totally inequitable situation which builds health inequalities into the system when it should be government policy to eradicate health inequalities.

2) Appeal point under Ground Three: 'The Institute has exceeded its powers'.

The second focus of our appeal lies in NICE's discrimination against patients who are 'sero-negative' for rheumatoid factor. Discriminating against this group of patients, comprising up to 25-30% of the RA population and for whom Rituximab may not be a suitable treatment option, is, in our view, a clear infringement of a patient's human rights and also the Disability Discrimination Act.

European Human Rights Convention
Article 1
Purpose
The purpose of the present Convention is to promote, protect and ensure the full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities, and to promote respect for their inherent dignity.
Persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others.

Article 2
Definitions
For the purposes of the present Convention:
"Discrimination on the basis of disability" means any distinction, exclusion or restriction on the basis of disability which has the purpose or effect of impairing or nullifying the recognition, enjoyment or exercise, on an equal basis with others, of all human rights and fundamental freedoms in the political, economic, social, cultural, civil or any other field. It includes all forms of discrimination, including denial of reasonable accommodation;

"Reasonable accommodation" means necessary and appropriate modification and adjustments ***not imposing a disproportionate or undue burden, where needed in a particular case, to ensure to persons with disabilities the enjoyment or exercise on an equal basis with others of all human rights and fundamental freedoms.***

It is very well established in clinical trials of all currently licensed TNF inhibitors and on the basis of clinical experience that sero-negative RA patients respond equally as well as those who are sero-positive to anti-TNF therapies. This is not the case for the B cell depleting therapy rituximab (RTX), the only option after failure of an anti-TNF that is recommended by current NICE guidance. Clear cut data emerging from trials and experience is that B cell depletion therapy is not as successful in sero-negative RA patients. In a sub-analaysis of the REFLEX study by Cohen et al, presented at the ACR meeting in Boston in November 2007 and published in abstract form, the difference in rate of progression of structural damage to joints between 201 placebo-treated patients and 298 rituximab treated patients was similar for nearly all subgroup analyses according to different baseline characteristics with the notable exception of sero-positivity for anti-CCP2. >50% inhibition of structural damage was observed in significantly more anti-CCP2 +tve patients (0.85 RTX vs 2.21 placebo) but not in anti-CCP – tve patients ((0.97 (n=33) vs. 1.09 (n=21)).

In routine clinical practice, for a sero-negative patient failing to respond to an anti-TNF treatment, the logical and preferred treatment options would be either to switch to an alternative anti-TNF or to abatacept. The consequence of the current FAD, together with recent NICE guidance that did not recommend the use of abatacept after failure of a first anti-TNF, is that there may be no viable treatment option, according to NICE guidance, for a sero-negative RA patient after a first anti-TNF failure. This view "***imposes a disproportionate or undue burden, in a particular case,*** *in failing* ***to ensure to persons with disabilities (ser-negative RA) the enjoyment or exercise on an equal basis with others of human rights and fundamental freedoms",*** *namely access to treatments that may be efficacious.* Furthermore, the recommendations of NICE in the current FAD fail to capture the benefits of treatment that may be experienced by the families and carers of patients and this too, in our view, is discriminatory.

Therefore, the FAD represents a serious infringement upon Articles 1 and 2 of the European Human Rights convention.

The public, physicians and patient populations understand well that those responsible for making decisions about resourcing of the nations' healthcare needs have to take wise and informed decisions about best use and allocation of a finite resource in order to best meet the necessary health needs. However, the decisions taken by NICE in the current FAD, and recently regarding abatacept for the treatment of RA, have placed the approximately 1% of the citizens of the United Kingdom at a significant disadvantage over many of their European and North American counterparts and, in effect, deny any efficacious treatment to a proportion.

It seems to us to be irreconcilable with the recent report from Lord Darzi that placed the patient experience, patient satisfaction and patient reported outcomes at the heart of the drive for quality. Crucially that "patients' own assessments of the success of their treatment and the quality of their experiences will have a direct impact on the way hospitals are funded." Moreover, the recommendations of NICE in the current FAD fail to capture the benefits of treatment that may be experienced by the families and carers of patients. This is a lamentable situation and one for which a generation of patients with RA will pay a heavy price, as indeed will our society.

Yours sincerely,

Attached to this Appeal document is a list of signatures of NRAS members and supporters who have signed their name via our website in the last 4/5 days along with views and comments in support of the NRAS Appeal. The list numbers : 1972 people and we have also appended their comments separately.