Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: **British Society for Rheumatology**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √ I have been involved in clinical trials of Golimumab
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- Member of British Society for Rheumatology, past member of the clinical affairs committee. Presently speciality Advisor for Rheumatology for [redacted] Region
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Rheumatoid arthritis "RA" is a "chronic inflammatory condition". Its management has been well described in a number of recent clinical guidelines. NICE clinical guideline number 79, Rheumatoid Arthritis in Adults 2009, BSR Guidelines (dated 2009) for the Management of RA.

In outline:

RA typically affects the small joints of the hands and feet, usually symmetrically, although any synovial joint can be affected. There are approximately 400,000 people with RA in the UK. The incidence is low with approximately 12,000 new cases each year. RA affects two to four times more women than men. RA most commonly affects people in their 70's but can develop at any age. RA commonly presents very acutely. It typically affects people between 35-55 years of age. Drug management aims to relieve symptoms and to modify the disease process.

The disease if left untreated leads to significant joint damage resulting in the need for joint replacement and significant and progressive functional impairment. Aggressive disease modification slows or stops radiological progression. Radiological progression is closely correlated with progressive functional impairment. Approximately one third of people who develop acute rheumatoid arthritis will stop work within two years of onset. The total cost of RA in the UK has been estimated at between £3.8 and £4.75 billion pounds per year. Rheumatoid Arthritis is also associated with significant systemic features such as fatigue and weight loss. These occur early in the course of the disease and may predominate, over shadowing the joint manifestations at first. Rheumatoid Arthritis can also be complicated or present as a systemic disease such as vasculitis, which is a life threatening complication. The systemic affects of rheumatoid arthritis have been shown to lead to serious constitutional and life threatening complications which impact significantly on the lives of patients with rheumatoid arthritis, further reinforcing present management strategy of early and aggressive treatment with disease modifying agent and if appropriate, biologic agents such as TNF Alpha Blockers.

Patients with chronic inflammatory diseases such as RA, are at increased risk of developing multiple co-morbid conditions. The risks of developing coronary artery disease, Insulin resistance, anaemia, infection and malignancy – lymphoma in particular, are increased among patients with RA.

Multiple studies have shown that patients with RA have a significantly increased risk of developing heart disease that is independent of traditional risk factors such as diabetes, alcohol abuse, hyperlipidaemia, blood pressure and body mass index. The consequences of untreated or inappropriately treated RA may lead to premature mortality; the mean life expectancy for patients with RA is reduced by between 5-10 years. Increasing evidence suggests that chronic inflammation associated with uncontrolled or inadequately controlled RA contributes to the development of these long term complications.

Healthcare professionals agree that patients should be seen by a Rheumatologist as soon as the disease presents and that the disease should be treated aggressively initially with standard disease modifying anti rheumatic drugs "DMARDS".

DMARDS commonly used at first include Methotrexate, Sulphasalazine, Hydroxychloroquine, Leflunomide etc. Various guidelines have been published as indicated above, both by the BSR and NICE as indicated above and below.

Patients with RA should be seen by a Rheumatologist as soon as possible. Once the diagnosis has been confirmed most rheumatologists will offer a combination of DMARDS "including Methotrexate and at least one other DMARD, plus short term Glucocorticoids" as soon as possible. Ideally within three months of the onset of persistent symptoms. In those patients who respond to combination and DMARD mono therapy, their drug doses may be cautiously reduced to levels that maintain disease control. Unfortunately, despite this aggressive approach to the management of patients with RA, there are a significant number of patients who fail to respond, clinically to this use of DMARDS and continue to display significant ongoing joint damage and systemic features. There is also increasing evidence that even those patients who appear to "clinically respond" continue to have evidence of ongoing joint damage. The aggressive management of patients with RA, with DMARD's has certainly significantly improved the prognosis of patients with this disease, but there continues to be considerable morbidity and as indicated above, increased risk of associated co-morbid conditions.

These patients with uncontrolled RA whose disease cannot be controlled by the use of DMARDS and Steroids should now be considered for treatment with biologic agents. The use of these biologic agents such as Adalimumab, Etanercept and Infliximab have been appraised by NICE and also guidelines on when these agents should be started, continued and withdrawn in various BSR guidelines.

NICE Guidance, the use of biologics include:

- **Rheumatoid Arthritis (Refractory) – Abatacept (TA141)**
- **Rheumatoid Arthritis (Refractory) – Rituximab (TA126)**
- **Rheumatoid Arthritis – Adalimumab, Etanercept and Infliximab (TA130)**
- **Rheumatoid Arthritis – Certolizumab, PEGOL**
- **Rheumatoid Arthritis – Etanercept and Infliximab (Partially replaced by TA130)**

Those patients who do not respond to standard DMARD therapy and fulfil the criteria for the introduction of a biologic agent, as according to NICE and the BSR guidelines, should be treated as outlined in these guidelines.

Clinical experience in the use of biologic therapies, by consultant rheumatologists and healthcare professionals have shown how a significant number of these difficult to manage patients with RA, respond dramatically to the introduction of a biologic agent. Many to them returning to normal function!. By controlling disease activity in these patients who fail standard DMARDS, has a significant impact on their long term morbidity and mortality. Not only does the direct costs of managing these patients needs to be considered, but also, if the disease is not controlled, the costs of joint replacement and frequent hospitalisation, the direct cost of managing the co-morbidities associated with prolonged use of high dose Steroids (which are frequently used in these patients, not controlled by standard DMARD therapy) such as cardio and cerebral vascular disease, osteoporotic fracture, diabetes, infection and cataracts should also be considered, and included in any economic evaluation.

It has also been shown that at an earlier stage in the disease, the threat and loss of income from being unable to work (a risk that reaches 50% after five years of disease), the increased risk of divorce and the cost of child care are other factors that result in considerable expense. As the BSR has commented to NICE in the past, the above factors need to be weighed against the cost of successful biologic therapy in such stipulations and its felt that to be able to truly tackle the burden of RA, clinicians and patients should have access to the broadest range of efficacious biologic agents including golimumab. Those patients who fail standard and aggressive DMARD therapy defined as "previous treatment failures" and thus present our most difficult to manage patients. As indicated above and in various NICE appraisal and BSR guidelines, these treatment options offer significant benefits. There are also associated risks in the use of these biologic agents.

The BSR has developed the "BSR Biologics Register". This register was developed and has been an enormous success to determine whether there was an increased risk of certain cancers or other potential side effects from the use of biologics. Presently this doesn't appear to be a significant issue. The register has had many other uses, in particular looking at the benefits of these drugs and the risks such as infection. Patients on biologics are at increased risk of both minor and serious infection and therefore these patients need to have continued close follow up in secondary care. It is the opinion of most rheumatologists that biologics should not be prescribed in primary care without the support and knowledge of their local rheumatology unit. Shared care in the community should be aimed for, if necessary, once the patient has their disease controlled.

Biologic therapies have now been in routine use for several years. There are considerable geographical variations in the frequency of prescribing these agents. The reasons for this are varied but primarily, include lack of resources. Biologics are frequently used out of licence, for many other rheumatological conditions but if so, their use usually has to be approved by the local Therapeutics Committee.

There are a number of guidelines available as indicated above for the management of rheumatoid arthritis and use of biologic agents. The evidence for these guidelines has been well studied (NICE/BSR etc) and I therefore do not feel that there is any need to further discuss at this time.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The introduction of tumour necrosis factor (TNF) inhibitors have constituted a major advance in the treatment of RA.

Treatment with the four currently available TNF Alpha Inhibitors (Adalimumab, Etanercept, Infliximab, Certolizumab PEGOL) in combination with Methotrexate (MTX) can significantly improve the signs and symptoms of disease as outlined in the related technology appraisal in the use of biologic agents for the treatment of rheumatoid arthritis (TA126, TA130, TA141 and more recently, TA 186).

Biologic agents have been shown to significantly improve the signs and symptoms of disease, decrease the progression of joint damage and improve physical function and health related quality if life.

Although all these agents have shown similar efficacy in clinical trials, they have different modes of action and exhibit individual pharmacokinetics, safety and efficacy profiles and patient responses to them in clinical practice may be variable. Some patients may respond to one anti TNF but not to another, while others may discontinue therapy because of poor tolerability or loss of efficacy over time.

The development of TNF Alpha inhibitors has proven to be a major advance in the treatment of not only RA but other inflammatory musculo skeletal conditions such as psoriatic related arthropathy and ankylosing spondylitis.

Although many patients derive significant benefit from TNF Alpha Inhibitors, there remains a population of patients who do not achieve a satisfactory clinical response, but there are other currently available agents.

Despite a limited amount of empiric evidence, clinical experience has shown that patients often respond to a second TNF Alpha Inhibitor when they experience lack of efficacy or waning of response to the first agent.

Thus, the response of individual patients to TNF Alpha Inhibitors are not homogeneous. There is, therefore a group of patients who will not respond to our standard three TNF Alpha agents which are used presently, Adalimumab, Etanercept and Infliximab. More recently the introduction of Certolizumab PEGOL, a pegylated Fab-fragment of an anti TNF Alpha antibody, has recently been approved by NICE (TA186). I believe that NICE should consider the approval of Golimumab and approve its use as an additional therapeutic option for patients who are not responding adequately to current available anti TNF agents in patients who have failed previous anti rheumatic drugs.

The currently available anti TNF agents are administered either intravenously or subcutaneously. The subcutaneous agents are administered twice a week to once every two weeks. Golimumab will provide the option of once a month S/C administration which will be more convenient for patients who are currently injecting themselves more frequently.

Golimumab is a monoclonal antibody (mAb with an IgG1 heavy chain isotype (G1m(Z) allotype) and a Kappa light chain isotype. Golimumab was derived by immunising mice that were transgenic for part of the human Ig repertoire with human TNF Alpha, and applying conventional cell fusion technology to generate a hybridoma cell line that secreted a human mAb. There are extensive non clinical studies looking at the pharmacology, pharmacokinetics and metabolism in animals which led to its use in humans. The efficacy and safety of Golimumab has been studied in a comprehensive Phase 3 development programme that included more than 2000 patients with moderate to severe active rheumatoid arthritis, active psoriatic arthritis and active ankylosing spondylitis. In these Phase 3 rheumatoid arthritis trials , Golimumab has been shown to be effective regardless of prior treatment experience which included patients inadequately responding to Methotrexate and patients previously treated with anti TNF agents.

In April 2009 Golimumab was approved by the US Food & Drug Administration (FDA) and the Health Canada for the treatment of moderately to severe active rheumatoid arthritis, active psoriatic arthritis and active ankylosing spondylitis.

Golimumab , 50mg subcutaneous injection once monthly, was approved for use in the European Union in July 2009 Bulletin, in combination with Methotrexate, for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when response to disease-modifying anti rheumatic drugs (DMARD) therapy including Methotrexate, has been inadequate.

Golimumab has also been shown to improve physical function in this patient population. It has also been approved as indicated above, for use also in patients with psoriatic arthritis and ankylosing spondylitis but that will not be discussed any further at this time.

Three Phase 3 trials of subcutaneous administration of Golimumab have been conducted in three different sub groups of patients with RA.

The GO-BEFORE trial was designed to assess the efficacy and safety of Golimumab administered every four weeks as mono therapy or in combination with Methotrexate in patients with active RA who had not been previously treated with MTX (MTX-naive).

The GO-AFTER trial was designed to assess the efficacy of an anti TNF Alpha agent in patients with active RA despite previous treatment with other TNF Alpha antagonist (S). This study was the first double-blind, placebo controlled prospect to try and demonstrate the efficacy of an anti TNF Alpha agent in patients with

active RA despite previous treatment with other TNF Alpha antagonists (s), and supports the use of Golimumab in patients who have experienced loss of efficacy or are intolerant to treatment with another TNF Alpha inhibitor. This will not be considered further as this is not the purpose of this technology appraisal.

The GO-FORWARD trial which will be discussed at the purpose of this technology appraisal was designed to assess the efficacy and safety of Golimumab in patients with active RA despite MTX therapy.

This was a multi centre double blind, placebo controlled trial of 44 patients including both Golimumab mono therapy and Golimumab plus MTX combination treatment arms. Patients could enter early escape if they did not achieve at least 20% improvement in both swollen and tender joint counts at week 16. The co primary end points with a proportion of patients who achieved the ACR20 at week 14 and the improvement from baseline in the health assessment questionnaire (HAQ) at week 24. Both primary and secondary end points were met. Both 50mg Golimumab and MTX and 100mg Golimumab plus MTX were comparable in efficacy and achieved statistical significant for all secondary end points, end points at 24 weeks including ACR50, ACR70, DAS 28 (using CRP) responders and DAS 28 (CRP) remission.

Results from this trial confirm the efficacy of Golimumab in patients with active RA despite MTX therapy that was observed in the Phase 2 trial and demonstrate that 50mg Golimumab or 100mg Golimumab administered every four weeks in combination with MTX, significantly reduced signs and symptoms and improved physical function in patients with RA.

During these clinical trials it has been shown that the safety profile of Golimumab is comparable to those of other TNF Alpha inhibitors, as a class, TNF Alpha inhibitors are associated with an increased risk of developing opportunist infections and lymphoma, although the increased incidents of lymphoma observed in patients with RA treated with these drugs may not be higher than that which occur in the overall population of patients with RA. Reactivation of Latent Tuberculosis (TB) can occur in patients with TNF Alpha inhibitors; therefore, routine TB screening and treatment Latent TB, if present, is recommended before initiating treatment with any agent in this therapeutic class.

In the Golimumab Phase 2 trials, the most common adverse events reported were nausea, headache, injection site erythema and worsening of RA disease activity. No cases of TB or lymphoma occurred, and the overall rate of infection in Golimumab treated patients was comparable to that of the placebo group.

Adalimumab was also well tolerated in all Phase 3 trials of subcutaneous Golimumab, and reported adverse events were consistent between the RA, AS and PsA study populations. Serious adverse events were reported in 2.3% to 9.7% of patients among all treatment arms and serious infections were reported in 0.7% to 5.6% of patients.

Antibodies against Golimumab have only been detected in a small number of patients in all studies. Not of the patients who were positive for antibodies to Golimumab experienced a severe injection site reaction or serious adverse events and non discontinued the study agent because of lack of efficacy. Rates of anti Golimumab antibody detection reported for the Phase 3 trials were similar to all less than those observed for other anti TNF monoclonal antibodies. Clinical trials had ranged from 3.7% (GO-AFTER) to 4.6% (GO-REVEAL) of Golimumab treated patients.

Therefore Golimumab is a new human anti TNF Alpha monoclonal antibody that blocks the action of TNF Alpha both in vitro and animal disease models.

Golimumab has been confirmed to be an effective treatment for patients with RA (including those naive to MTX, those inadequately responsive to MTX and those previously treated with a TNF inhibitor), AS, PsA in Phase 3 clinical trials that have included traditional measures of disease activity and functional decline.

The safety and tolerability of Golimumab are comparable to that of other TNF Alpha inhibitors. With subcutaneous administration of Golimumab only necessary every four weeks, this offers an additional advantage to patients and therefore offers effective disease activity control with less frequent dosing than the other commercially available SC TNF Alpha antagonists.

Structural progression after 52 weeks of Golimumab therapy has been measured but the results are not yet available. Guidelines as to starting biologic therapy currently require a person to have a DAS 28 score greater than 5.1 on two occasions a month apart having previously failed two standard DMARDS.

The BSR has discussed at length this point in their article "Criteria for the first Biological Therapy" (rheumatology 2009). There is a move to reduce the DAS score down to 3.2 to make sure that some deserving patients are not prevented from receiving biologic therapy because they may not fulfil the current criteria. This is particularly true if these patients are on a significant dose of Steroids.

In summary, Golimumab new anti TNF Alpha inhibitor that has been shown to be an effective treatment for patients with RA. The safety and tolerability of Golimumab are comparable to that of other TNF Alpha inhibitors. Subcutaneous administration every four weeks offers less frequent dosing than any other commercially available subcutaneous TNF Alpha antagonists.

The BSR believes that there is a need for greater diversity within this therapeutic field including the fact that greater competition in the market for these highly efficacious class of drugs is anticipated to have benefits in perhaps even driving down costs.

There is also evidence from the GO-BEFORE trial that Golimumab is an effective treatment for RA and that it also works as mono therapy, allowing those patients who become sensitive to Methotrexate to still benefit from anti TNF therapy.

There is also evidence from the GO-AFTER trial and this was also the first double blind placebo controlled prospective trial to demonstrate the efficacy of an anti TNF Alpha agent in patients with active RA despite previous treatment with other TNF Alpha antagonists and its supported the use of Golimumab in patients who have experienced loss of efficacy or were intolerant to treatment with another TNF Alpha inhibitor.

I believe that patients should be given the option of a range of cost effective treatments. BSR feel it is unethical to deny patients an alternative cost effective agent.

Final scope allowing patients different options of biological agent reflects the situation in real clinical practice.

Rheumatoid Arthritis is a severe multi system disorder which, if inadequately controlled, may result in enormous direct and indirect healthcare costs. Despite

the enormous therapeutic advances, a significant unmet need exists for patients who do not respond to the currently available agents.

It is my view that Golimumab would be an important addition to the therapeutic armoury needed to help patients with RA. Once monthly dosing regime offers greater flexibility to patients with RA who require a TNF Alpha blocker.

It is inappropriate to comment any further on trial designs in this short report but as indicated above, the outcome measures in the trials discussed above, demonstrate the efficacy of Golimumab in the management of rheumatoid arthritis and other rheumatological conditions and offers a convenient once monthly subcutaneous regime. There will also be the facility to give Golimumab intravenously – increasing its flexibility.
Recent publication of the 52-week results of the GO-FORWARD study in Annals Rheumatic diseases –June 2010

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any information that is not freely available in the journals or meeting abstracts.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
NICE guidance is important as it affects whether the drug will be funded by Primary care or not.
I am not aware , that the giving or monitoring of Golimumab differs significantly from the other biologic agents. Therefore no additional staff or training will be required.