The British Society for Rheumatology

Jeremy Powell,
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10th August, 2009

Dear Mr Powell,

Re: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Thank you for inviting us to submit evidence to this technology assessment.

The British Society for Rheumatology (BSR) exists to promote excellence in the treatment of people with arthritis and musculoskeletal conditions and to support those delivering it. As a professional association, BSR aims to improve standards of care in rheumatology. With over 1500 members, including clinicians, scientists, academics, trainees and allied health professionals, it seeks to enhance the skills of the rheumatology team through education and professional development opportunities. It also aims to ensure that those with an interest in rheumatology can access and contribute to the most up-to-date evidence base.

Enclosed are two submissions:

1) a summary of the relevant evidence from the BSR Clinical Affairs Committee based, in part, on Biologics Guidelines published by BSR in May 2009. (Note: for a copy of these guidelines, please contact us.) The lead author for this submission was [redacted];
2) an updated analysis on sequential use of anti-TNF therapies from the BSR Biologics Register (BSRBR), corresponding author [redacted].

This submission is supported by the Arthritis and Musculoskeletal Alliance (ARMA) who were also involved in its preparation. ARMA has 34 member organisations representing a broad range of interests across service user, professional and research groups working in the field of musculoskeletal conditions.

Yours sincerely,

[redacted]

Encl:
1. BSR Clinical Affairs Committee submission
2. BSRBR submission
2a. Appendix 1: Hyrich KL et al. Arth Rheum 2007; 56:13-20
2b. Appendix 2: Hyrich KL et al. Rheumatology (Oxford) 2008; 47: 1000-1005
2c. Appendix 3: Harrison MJ et al. Health Qual.Life Outcomes [under review]. 2009
3. Letter of support from ARMA

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Abatacept, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor.

Submission on behalf of the British Society for Rheumatology Clinical Affairs Committee, chair [redacted]

Introduction

In 2007 NICE published a Final Appraisal Determination again concluding that patients who have failed on their first anti-TNF agent due to lack or loss of response should not be allowed to have access to a second anti-TNF agent because this was determined not to be a cost-effective use of NHS resources [1]. The NICE Appraisal Committee accepted that the reviewed evidence showed that a second anti-TNF agent was clinically effective, but their health economic analysis suggested that this approach was not cost-effective. This leaves the original guidance unchanged with regard to a second anti-TNF drug, and leaves NHS patients who fail on their first anti-TNF agent the choice of either rituximab, or returning to conventional DMARDs.

Measures of cost effectiveness in relation to switching

Data from the British Society for Rheumatology Biologics Register (BSRBR) has shown that patients who switch anti-TNF therapy following the failure of their first anti-TNF therapy show a significantly better improvement in Health Assessment Questionnaire (HAQ (0.15)) than those who stay on their first anti-TNF therapy (in spite of inadequate response) or stop the anti-TNF therapy [2]. These data hold true despite the fact that patients have had disease for 11 years, failed on a mean of 4 DMARDs, and concurrent methotrexate was only being used in 47% of patients. Other observational studies show greater HAQ improvements on switching from a failing first anti-TNF agent to a second (0.33 to 0.52 in the ReAct study [3]).

There is therefore clear evidence of a clinical response with a 2nd anti-TNF treatment after failure of primary treatment. Some patients may not respond as well as others and recent data suggests this may be related to the development of auto-antibodies to the biologic drugs [4]. Nevertheless, the difficulty is in measuring the clinical benefits for economic modelling.

Currently, there is not an accepted single measure for evaluating health utility in rheumatoid arthritis. Direct and indirect measures have been evaluated and the HAQ has been used most widely in modelling. This approach was criticised by Scott and colleagues [5] who found a poor correlation between HAQ scores and the indirect utility measure EuroQol (EQ-5D) in 321 patients with rheumatoid arthritis (RA).

In contrast, Ariza-Ariza and colleagues [6] found a close correlation between HAQ and EQ-5D in 260 RA patients. They found a poor correlation between EQ-5D and DAS 28 but a similar correlation between both HAQ and DAS28 and the Time Trade-Off (TTO) instrument of utility. Interestingly however, there was only a moderate correlation between the mean change in EQ-5D and HAQ.

Witney and colleagues [7] also found a stronger correlation between HAQ and EQ-5D and only a moderate correlation between HAQ and the direct utility measures TTO and Standard Gamble (SG). One reason for the disparity in these measurements suggested by the researchers is that patients with established RA report a higher health utility on the EQ-5D indicating that such patients have a higher acceptance of their illness [8] and less depression [9].

In relation to the health economic analyses of sequential anti-TNF therapy, the previous appraisal committee were concerned that the Birmingham Rheumatoid Arthritis Model (BRAM), modelled predominantly on HAQ changes in the BSRBR, found very high incremental cost-effectiveness ratios (ICERs) and failed to approve the use of a second anti-TNF. In our view the HAQ response in these patients significantly underestimates the clinical response.

In patients with a HAQ in the upper part of the range, the relationship between utility and HAQ appears to be less well defined. Kobelt and colleagues [10] found that the EQ-5D was able to discriminate between patients with different HAQ scores but only in ACR functional class II. Witney and colleagues found a greater variability in SG, TTO and EQ-5D utility scores in those with higher HAQ scores. Bansback and colleagues [11] also found the difference between actual and predicted EQ-5D utility was greater in those with a HAQ score $\geq$ 2.5 and concluded that the HAQ is a suboptimal measurement compared with a direct measurement of health utility.

In the BSRBR the duration of disease is greater and the mean HAQ scores are higher than in published clinical trials of anti-TNF therapy. For example in the ReACT trial [3] the mean disease duration prior to first anti-TNF was 11 years with a mean HAQ score of 1.6; HAQ scores improved by approximately –0.5 and DAS scores by approximately –2.0. In the DREAM study [12] disease duration was between 6 and 7.7 years and baseline HAQ scores between 1.3 and 1.4. The HAQ scores improved by approximately –0.4 and DAS scores by approximately –1.8. In the BSRBR data of second anti-TNF response, the mean duration of disease is greater than 14 years with a base line HAQ of 2.1. [2,23]. The clinically significant fall in DAS scores is not reflected in the reduction in HAQ score of only –0.15.

These data indicate that the clinical response and improved utility following anti-TNF therapy in those with significant disability is not reflected in the HAQ scores. Patients with established longstanding disease often have irreversible damage and deformity in their joints. However, treating active synovitis – reflected in high DAS scores – in this group of patients will have a significant benefit in utility with little effect in HAQ score.

The importance of including clinical response, as well as disability, is reflected in the study by Brennan and colleagues [13]. They modelled the clinical response to the disability/utility improvement rather than using average improvement in HAQ scores. They also differed from the BRAM in modelling the concept of withdrawal unless an adequate clinical response was achieved. The result of this study indicated that using a second anti-TNF after failure of the first drug was cost effective using the current parameters accepted by NICE.

Choice of Rituximab after failure of a first anti-TNF agent

The following are concerns about rituximab being the only available biological drug following the failure of a first anti-TNF agent:

1. There is a substantial and growing database on the long-term efficacy of anti-TNF therapy on disease activity, function and quality of life. There is also evidence for long-term inhibition of radiological progression in responders to anti-TNF therapy, and early data supporting reduction in work disability, and improvements in cardiovascular morbidity and mortality.
   There is no comparable data for rituximab.

2. There is a substantial and growing database on the long-term safety of anti-TNF therapy. Data from the BSRBR has shown that, compared to standard DMARD therapy, the risk of serious infections may be increased in the first 3-6 months of treatment but this risk seems to decrease over time [14]. Preliminary data from large observational studies have not found a significant increased risk of cancer [15].

   There are concerns that recurrent infusions of rituximab may lead to persistent decreases in immunoglobulin levels, and though so far no increased infection risk has emerged, the concerns remain. The effect of B-cell depletion on future treatment options is also unknown.

3. The response of seronegative patients to rituximab may be diminished or even absent [16,17]. Indeed EULAR guidelines suggest that rituximab should not be used in seronegative disease [18]. By contrast, serological status does not determine the response to anti-TNF therapy [19].

4. The EMEA licence for rituximab states that it must be given in combination with methotrexate, which leaves methotrexate intolerant individuals with no treatment option. Adalimumab and etanercept are licensed for use in patients who are unable to take methotrexate.

5. Rituximab can only be given in prolonged intravenous infusions in hospital facilities with resuscitation equipment available. This removes choice from patients who would like to manage their condition at home.

Choice of supportive care after failure of a first anti-TNF agent

There are concerns about patients returning to conventional DMARDs, steroids or palliative care following the failure of biological therapies. There is no evidence to show that this approach is helpful.

- The BeSt trial has demonstrated that patients who fail on methotrexate are unlikely to respond to other conventional DMARDs [20]. All NHS patients will have been exposed to methotrexate prior to going onto anti-TNF, therefore returning to conventional DMARDs following the failure of anti-TNF is very unlikely to be helpful. Data from the British Rheumatoid Arthritis Outcomes Study Group shows that patients on either symptomatic or aggressive treatment strategies show progressive deterioration in HAQ over three years of follow up [21].

- Patients in the BSRBR who switched to a second anti-TNF agent after the failure of the first showed significant improvements in HAQ over 1 year of follow-up, whereas those who stopped and returned to conventional DMARDs or palliative treatment showed no change in HAQ over the year [2].

- Long-term steroid therapy for patients failing biologics is an option where the advantages are soon heavily outweighed by the disadvantages. The NICE RA Management Guidelines advise against the use of long-term steroids, and suggest that a variety of tactics, including the use of biologics, should be employed to try to avoid this [22].

Taken together, these data suggest that returning to conventional DMARDs, steroids or palliative care following the failure of biologics is not a helpful option.

Choice of a second anti-TNF agent after failure of a first anti-TNF agent

There is evidence to show that secondary non-responders (those who have lost response) show better efficacy on a second anti-TNF agent than primary non-responders (those who never responded). The ReACT study found that secondary non-responders are more likely to respond to a second anti-TNF agent compared with a primary non-responder [3]. Data from the BSRBR demonstrate that patients who fail to respond to their first anti-TNF agent (primary non-responders) are more likely to have a similar response with their second [23].

A recent study addressing sequential use of the South Sweden Arthritis Treatment Group Register showed that first time switchers' response rates are somewhat below that of biologic naïve patients; further, 71% of first time switchers achieving a EULAR good or moderate response compared with 58% of second time switchers [24]. DAS remission rates were 16% in first time switchers compared with 6% in second switchers. Baseline predictors of response to treatment were lower age and HAQ score, high DAS and having stopped anti-TNF due to adverse events rather than inefficacy. This study suggests a diminishing response with second and third anti-TNF agents.

The BSR recommends that in RA patients who lack or lose response to their first anti-TNF agent, a second anti-TNF agent should be made available.

Rituximab in RA non-responders to anti-TNF

Current NICE guidelines [25] state that rituximab should be used

a. with methotrexate
b. in patients who have had an inadequate response to or intolerance of other DMARDs, including treatment with at least one anti-TNF therapy.
c. by physicians specialising in rheumatoid arthritis

It should be continued only if patients show an improvement in disease activity of 1.2 points or more. Repeat courses should be given with methotrexate and no more than 6 monthly.

This raises several questions:

i. Can rituximab be given without other DMARDs, or with alternatives to methotrexate?
ii. Should the eligibility and response criteria be modified?
iii. Should the suggested frequency of repeat infusions be modified?

i. Can rituximab be given without other DMARDs, or with alternatives to methotrexate?

The initial pivotal trial [26] included cyclophosphamide or methotrexate as the concomitant treatment. Although this was the initial open label trial, little difference existed between those treated with methotrexate and rituximab and those treated with cyclophosphamide and rituximab. In this trial, rituximab was also used as monotherapy with good efficacy, but this did not achieve significance versus placebo due to the small numbers in each group. The percentage figures for efficacy at 24 weeks are summarised in the table below.

Strategy	% achieving ACR20	% achieving ACR50	% achieving ACR70
Methotrexate	38	23	5
Rituximab alone	65	33	15
Cyclophosphamide and rituximab	76	41	15
Methotrexate and rituximab	73	43	23

Table 1. Efficacy of rituximab when used with a variety of other concomitant medications [19]

Recent data has suggested the possible role for leflunomide in patients intolerant of methotrexate [27,28]. There is very little data available regarding the combination of rituximab with other biologic therapies. In a small study with only 18 patients [29], patients were treated with etanercept and rituximab with good efficacy and no apparent significant increase in side effects with the etanercept discontinued a week before, and recommenced a week after the infusions. However, combination of other biologics has been associated with increased incidence of side effects, particularly infections, without increase in efficacy and therefore this area requires further research before any recommendation can be made [30].

ii. Should the eligibility and response criteria be modified?

All rituximab studies have enrolled patients with active RA. Some studies have only included those who have previously trialled anti-TNF therapy, whilst others have enrolled patients who have not had previous biologic therapy, with others including both groups of patients. The eligibility criteria for the major rituximab studies are similar: a swollen and tender joint count of equal to or more than 8 joints out of 68, an ESR of $\geq$ 28, and a CRP $\geq$ 1.5mg/dl. The Edwards et al trial stipulated that patients must be rheumatoid factor positive [26]. Other studies have not used this as an inclusion criterion but have only had small numbers of rheumatoid factor negative (seronegative) patients included.

Evidence suggests that seronegative patients do not respond as well to rituximab as patients who are rheumatoid factor positive (seropositive); however there may be some benefit in seronegative patients (see Table 10). One study failed to show significant response compared with placebo – but this study had 52% of patients achieved an ACR

20 on placebo [16]. Another study showed significant response in both groups but less in seronegative than seropositive patients (ACR 20 of 41% in seronegative and 54% in seropositive) [17].

Patients	Rituximab/ placebo	ACR 20 on Rituximab %	ACR20 on placebo %	P value	Reference number
RF pos %	79/79	54	19	<0.001	[10]
RF neg %	21/21	41	12	<0.001	[10]
RF pos	128/128	54	28	<0.003	[9]
RF neg	63/21	48	52	NR	[9]

Table 10. The responses of rheumatoid factor positive and negative RA patients to rituximab in two of the pivotal trials.

Preliminary data have shown that seropositivity to anti-CCP antibodies behaves in a similar fashion to seropositivity to RF [31], with greater responses in patients who are anti-CCP antibody positive than negative. Patients who convert to being seronegative for RF after their first infusion of rituximab appear to have a similar response as those who remain seropositive after their first infusion [32].

The BSR recommends that Rituximab should be given in patients with active rheumatoid arthritis who have failed biologics, or who are intolerant, or have contra-indication, to anti-TNF therapy. It should be borne in mind that patients who are rheumatoid factor positive or anti-CCP positive are more likely to respond to rituximab than patients who are negative for these antibodies.

The degree of EULAR responses in the pivotal trials show that a response of at least 1.2 DAS28 points is to be expected. The BSR recommends the use of at least a moderate EULAR response as the criterion for considering further treatments, for consistency with the BSR's recommendations for anti-TNF response criteria [33], and because EULAR response criteria are validated, whereas a DAS28 decrease of 1.2 irrespective of baseline DAS28 is not.

A delay of the assessment of response to 16 weeks should avoid the effect of the methylprednisolone infusion given with the rituximab, which is thought to last up to 8 weeks.

In a small study, patients who did not respond initially to rituximab also did not respond to further infusions [34]. In another small study, delaying the second treatment predicted a flare of disease, and gave a similar or enhanced secondary response [35]. An open label study looking at re-treatment has shown that a fixed re-treatment at 24 weeks and treating when a flare occurs have similar outcomes [36]. Data from Switzerland [37] suggests that the median duration of response in 83 RA patients was 12.7 months (inter-quartile range 9.4,22.3). There was some evidence that the efficacy of repeat infusions is cumulative. This was predicted by a good response to the first infusion.

The BSR recommends that RA arthritis patients on rituximab should be assessed for response at an interval of no less than 16 weeks. Patients who do not show at least a moderate EULAR response to the first treatment course should not be considered for re-treatment.

iii. Should the suggested frequency of repeat infusions be modified?

In an open follow up study in patients having more than one dose of rituximab [37] the interval between dosing was stable at 33 weeks (SD 10 weeks) in responders to the first dose. This was not different when stratified by anti-TNF therapy and non anti-TNF therapy exposed patients. The BSR recommends that re-treatment with rituximab in RA should be considered when initial treatment response of at least a moderate EULAR response has been lost. The frequency of infusion should be no less than 24 weeks.

Abatacept in RA non-responders to anti-TNF

Abatacept is a selective T cell co-stimulation modulator that blocks the CD80:CD28 or CD86:CD28 co-stimulatory signal that is required for full T cell activation. Abatacept is a fusion protein comprising the extracellular domain of human CTLA4Ig and a fragment of the Fc domain of human IgG1, produced by recombinant DNA technology in Chinese hamster ovary cells. CTLA4Ig has a greater affinity for CD80 or CD86 than it does for CD28, and as such it preferentially binds to these receptors, thus preventing normal co-stimulation via CD28. Abatacept is licensed for use in the UK in combination with Methotrexate for the treatment of moderate to severe rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other DMARDs including at least one TNF inhibitor.

NICE Technology Appraisal Guidance 141 [38] has not recommended abatacept for the treatment of patients with RA, on grounds of not being a cost effective use of NHS resources. This includes those in whom rituximab has failed or in whom rituximab is contra-indicated or not tolerated. The Summary of Product Characteristics does not recommend abatacept in combination with TNF blocking drugs because of an increase in overall and serious infections.

RA patients who have failed to tolerate or respond to TNF inhibitors have a limited therapeutic choice, between

- rituximab; or
- a return to non-biologic DMARDs alone or in combination;
- or corticosteroids.

RA patients who do not respond to therapies have a well documented poor outcome with respect to damage within the musculoskeletal system, and effects on cardiovascular and bone health, overall quality of life and life expectancy. In this context any treatment with proven efficacy is attractive, not least abatacept given the unique mechanism of action.

NICE did not dispute the fact that abatacept was efficacious in the treatment of RA. In order to move this debate on, it would therefore be important to focus on the following issues:

i. Is there any new evidence to show that the efficacy of abatacept may have been under-estimated in the treatment of RA?

ii. Is there any new evidence to show that abatacept might have advantages over other comparators (conventional DMARDs, anti-TNF therapies or rituximab) in treating all RA, or sub-groups of disease?

i. Evidence that the efficacy of Abatacept may have been under-estimated

1. Randomised, double blind, placebo controlled dose ranging add-on to methotrexate non-responders study [39-41].

   339 patients with active RA despite methotrexate were randomised to placebo (with methotrexate), abatacept 2mg/kg or 10 mg/kg (days 1, 15, 30 then every 30 days) up to 1 year, then all switched to open label abatacept 10mg/kg every 30 days. Significant improvement was seen at 1 year in ACR 20/50/70, L-DAS, HAQ and SF-36 (6 months data only) in 10mg/kg but not 2mg/kg compared with placebo. At 5 years, abatacept remained well tolerated and provided sustained benefits, with a higher proportion of patients achieving L-DAS and DAS-R at year 5 than year 1.

2. 'AIM': Randomised, double blind, placebo controlled add-on to MTX non-responders study [42-48].

   652 patients with active disease despite 15 mg or more of methotrexate were randomised to continue methotrexate and either have placebo, or abatacept 10 mg/kg (days 1, 15, 30 then every 30 days), then all placebo patients were switched to abatacept 10mg/kg.

   Significant improvement was seen in ACR 20/50/70, L-DAS, DAS-R, HAQ and radiographic outcome at 1 year versus placebo and sustained improvements at year 2 and 3 in all outcomes with suggestion of further incremental benefit on L-DAS, DAS-R and radiographic outcome, whereas the ACR20/50/70 had a plateau effect at year 2, and HAQ / SF-36 outcome had a plateau effect at year 1, with maintained responses at year 2.

3. 'ATTAIN': Randomised, double blind, placebo controlled switch to Abatacept in anti-TNF non-responders study [45,46,48-52]

   391 patients with active RA despite DMARDs and either current or prior anti-TNF (infliximab and etanercept) were included. DMARDS (75% on methotrexate) and oral prednisolone up to 10mg (70%) were continued but the dose was stable for 3 months. Anti-TNF therapy was stopped (former users 62%, current users 38%, washout etanercept 28 days and infliximab 60 days). Abatacept 10 mg/kg or placebo was given on days 1, 15, 30 then every 28 days, then all placebo patients were switched to abatacept 10mg/kg on day 141 ABA. A significant improvement was seen in ACR 20/50/70, L-DAS, DAS-R, HAQ and all SF-36 domains at 6 months. In the long term extension phase at year 2 and 3 incremental increases were seen in ACR 20/50/70, L-DAS, DAS-R, whereas no further improvements were observed in SF-36 and HAQ after 6 months. Placebo treated patients in the first 6 months showed similar benefit when switched to abatacept. The numbers of patients with greater L-DAS or DAS-R were higher if previously they had failed one anti-TNF agent as opposed to 2 anti-TNF agents. No difference in outcome was seen if the reason for stopping anti-TNF therapy was primary versus secondary non-response.

In conclusion, three large cohorts of patients have all shown that the maximum benefit from abatacept may be seen after the first year of treatment. The BSR recommends that abatacept should be available to RA patients who have failed to respond to other biological agents. Health economic analyses of abatacept should take into account the increase in efficacy that takes place after the first year of treatment.

ii. Evidence of advantages of abatacept over other comparators

Rituximab may be more effective in seropositive RA than seronegative disease. The only data the BSRBG have been able to find for this on abatacept is that presented by Bristol-Myers Squibb to the US Food and Drugs Administration. This covers efficacy in seronegative patients compared to seropositive patients in AIM (20% RF negative) and ATTAIN (27% RF negative) (see page 57 (AIM) and page 74 (ATTAIN)) [52]. In summary, ACR response rates were greater for abatacept than placebo in both seropositive and seronegative patients in both studies, with no obvious differences between the groups.

The ATTAIN study extension has shown that there is no difference in efficacy for patients demonstrating primary or secondary non-response on anti-TNF therapy, in contrast to the data for a second anti-TNF agent which may not be as effective under in primary compared with secondary non-responders.

If NICE eventually approves abatacept, it is likely that the drug would be used after the failure of rituximab in the UK. Genovese et al [49] report safety outcome in 185 patients with active RA despite rituximab therapy, who were then treated with another biologic drug over a median follow up period of 11 months. Of these 150 received an anti-TNF drug and 25 received abatacept. At the time of commencing the post-Rituximab biologic the majority had a CD19 count below the lower limit of normal. There is no report of an increase in the incidence of serious infections during post-Rituximab biologic exposure compared to during-Rituximab treatment. Also there were no opportunistic or fatal infections in the post-Rituximab biologic period. This is reassuring for the group of patients most likely to gain access to abatacept in the UK.

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Abatacept, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor.

Submission on behalf of the British Society for Rheumatology Clinical Affairs Committee, chair Dr Chris Deighton

Introduction

In 2007 NICE published a Final Appraisal Determination again concluding that patients who have failed on their first anti-TNF agent due to lack or loss of response should not be allowed to have access to a second anti-TNF agent because this was determined not to be a cost-effective use of NHS resources [1]. The NICE Appraisal Committee accepted that the reviewed evidence showed that a second anti-TNF agent was clinically effective, but their health economic analysis suggested that this approach was not cost-effective. This leaves the original guidance unchanged with regard to a second anti-TNF drug, and leaves NHS patients who fail on their first anti-TNF agent the choice of either rituximab, or returning to conventional DMARDs.

Measures of cost effectiveness in relation to switching

Data from the British Society for Rheumatology Biologics Register (BSRBR) has shown that patients who switch anti-TNF therapy following the failure of their first anti-TNF therapy show a significantly better improvement in Health Assessment Questionnaire (HAQ (0.15)) than those who stay on their first anti-TNF therapy (in spite of inadequate response) or stop the anti-TNF therapy [2]. These data hold true despite the fact that patients have had disease for 11 years, failed on a mean of 4 DMARDs, and concurrent methotrexate was only being used in 47% of patients. Other observational studies show greater HAQ improvements on switching from a failing first anti-TNF agent to a second (0.33 to 0.52 in the ReAct study [3]).

There is therefore clear evidence of a clinical response with a 2nd anti-TNF treatment after failure of primary treatment. Some patients may not respond as well as others and recent data suggests this may be related to the development of auto-antibodies to the biologic drugs [4]. Nevertheless, the difficulty is in measuring the clinical benefits for economic modelling.

Currently, there is not an accepted single measure for evaluating health utility in rheumatoid arthritis. Direct and indirect measures have been evaluated and the HAQ has been used most widely in modelling. This approach was criticised by Scott and colleagues [5] who found a poor correlation between HAQ scores and the indirect utility measure EuroQol (EQ-5D) in 321 patients with rheumatoid arthritis (RA).

In contrast, Ariza-Ariza and colleagues [6] found a close correlation between HAQ and EQ-5D in 260 RA patients. They found a poor correlation between EQ-5D and DAS 28 but a similar correlation between both HAQ and DAS28 and the Time Trade-Off (TTO) instrument of utility. Interestingly however, there was only a moderate correlation between the mean change in EQ-5D and HAQ.

Witney and colleagues [7] also found a stronger correlation between HAQ and EQ-5D and only a moderate correlation between HAQ and the direct utility measures TTO and Standard Gamble (SG). One reason for the disparity in these measurements suggested by the researchers is that patients with established RA report a higher health utility on the EQ-5D indicating that such patients have a higher acceptance of their illness [8] and less depression [9].

In relation to the health economic analyses of sequential anti-TNF therapy, the previous appraisal committee were concerned that the Birmingham Rheumatoid Arthritis Model (BRAM), modelled predominantly on HAQ changes in the BSRBR, found very high incremental cost-effectiveness ratios (ICERs) and failed to approve the use of a second anti-TNF. In our view the HAQ response in these patients significantly underestimates the clinical response.

In patients with a HAQ in the upper part of the range, the relationship between utility and HAQ appears to be less well defined. Kobelt and colleagues [10] found that the EQ-5D was able to discriminate between patients with different HAQ scores but only in ACR functional class II. Witney and colleagues found a greater variability in SG, TTO and EQ-5D utility scores in those with higher HAQ scores. Bansback and colleagues [11] also found the difference between actual and predicted EQ-5D utility was greater in those with a HAQ score $\geq$ 2.5 and concluded that the HAQ is a suboptimal measurement compared with a direct measurement of health utility.

In the BSRBR the duration of disease is greater and the mean HAQ scores are higher than in published clinical trials of anti-TNF therapy. For example in the ReACT trial [3] the mean disease duration prior to first anti-TNF was 11 years with a mean HAQ score of 1.6; HAQ scores improved by approximately –0.5 and DAS scores by approximately –2.0. In the DREAM study [12] disease duration was between 6 and 7.7 years and baseline HAQ scores between 1.3 and 1.4. The HAQ scores improved by approximately –0.4 and DAS scores by approximately –1.8. In the BSRBR data of second anti-TNF response, the mean duration of disease is greater than 14 years with a base line HAQ of 2.1. [2,23]. The clinically significant fall in DAS scores is not reflected in the reduction in HAQ score of only –0.15.

These data indicate that the clinical response and improved utility following anti-TNF therapy in those with significant disability is not reflected in the HAQ scores. Patients with established longstanding disease often have irreversible damage and deformity in their joints. However, treating active synovitis – reflected in high DAS scores – in this group of patients will have a significant benefit in utility with little effect in HAQ score.

The importance of including clinical response, as well as disability, is reflected in the study by Brennan and colleagues [13]. They modelled the clinical response to the disability/utility improvement rather than using average improvement in HAQ scores. They also differed from the BRAM in modelling the concept of withdrawal unless an adequate clinical response was achieved. The result of this study indicated that using a second anti-TNF after failure of the first drug was cost effective using the current parameters accepted by NICE.

Choice of Rituximab after failure of a first anti-TNF agent

The following are concerns about rituximab being the only available biological drug following the failure of a first anti-TNF agent:

1. There is a substantial and growing database on the long-term efficacy of anti-TNF therapy on disease activity, function and quality of life. There is also evidence for long-term inhibition of radiological progression in responders to anti-TNF therapy, and early data supporting reduction in work disability, and improvements in cardiovascular morbidity and mortality.
   There is no comparable data for rituximab.

2. There is a substantial and growing database on the long-term safety of anti-TNF therapy. Data from the BSRBR has shown that, compared to standard DMARD therapy, the risk of serious infections may be increased in the first 3-6 months of treatment but this risk seems to decrease over time [14]. Preliminary data from large observational studies have not found a significant increased risk of cancer [15].

   There are concerns that recurrent infusions of rituximab may lead to persistent decreases in immunoglobulin levels, and though so far no increased infection risk has emerged, the concerns remain. The effect of B-cell depletion on future treatment options is also unknown.

3. The response of seronegative patients to rituximab may be diminished or even absent [16,17]. Indeed EULAR guidelines suggest that rituximab should not be used in seronegative disease [18]. By contrast, serological status does not determine the response to anti-TNF therapy [19].

4. The EMEA licence for rituximab states that it must be given in combination with methotrexate, which leaves methotrexate intolerant individuals with no treatment option. Adalimumab and etanercept are licensed for use in patients who are unable to take methotrexate.

5. Rituximab can only be given in prolonged intravenous infusions in hospital facilities with resuscitation equipment available. This removes choice from patients who would like to manage their condition at home.

Choice of supportive care after failure of a first anti-TNF agent

There are concerns about patients returning to conventional DMARDs, steroids or palliative care following the failure of biological therapies. There is no evidence to show that this approach is helpful.

- The BeSt trial has demonstrated that patients who fail on methotrexate are unlikely to respond to other conventional DMARDs [20]. All NHS patients will have been exposed to methotrexate prior to going onto anti-TNF, therefore returning to conventional DMARDs following the failure of anti-TNF is very unlikely to be helpful. Data from the British Rheumatoid Arthritis Outcomes Study Group shows that patients on either symptomatic or aggressive treatment strategies show progressive deterioration in HAQ over three years of follow up [21].

- Patients in the BSRBR who switched to a second anti-TNF agent after the failure of the first showed significant improvements in HAQ over 1 year of follow-up, whereas those who stopped and returned to conventional DMARDs or palliative treatment showed no change in HAQ over the year [2].

- Long-term steroid therapy for patients failing biologics is an option where the advantages are soon heavily outweighed by the disadvantages. The NICE RA Management Guidelines advise against the use of long-term steroids, and suggest that a variety of tactics, including the use of biologics, should be employed to try to avoid this [22].

Taken together, these data suggest that returning to conventional DMARDs, steroids or palliative care following the failure of biologics is not a helpful option.

Choice of a second anti-TNF agent after failure of a first anti-TNF agent

There is evidence to show that secondary non-responders (those who have lost response) show better efficacy on a second anti-TNF agent than primary non-responders (those who never responded). The ReACT study found that secondary non-responders are more likely to respond to a second anti-TNF agent compared with a primary non-responder [3]. Data from the BSRBR demonstrate that patients who fail to respond to their first anti-TNF agent (primary non-responders) are more likely to have a similar response with their second [23].

A recent study addressing sequential use of the South Sweden Arthritis Treatment Group Register showed that first time switchers' response rates are somewhat below that of biologic naïve patients; further, 71% of first time switchers achieving a EULAR good or moderate response compared with 58% of second time switchers [24]. DAS remission rates were 16% in first time switchers compared with 6% in second switchers. Baseline predictors of response to treatment were lower age and HAQ score, high DAS and having stopped anti-TNF due to adverse events rather than inefficacy. This study suggests a diminishing response with second and third anti-TNF agents.

The BSR recommends that in RA patients who lack or lose response to their first anti-TNF agent, a second anti-TNF agent should be made available.

Rituximab in RA non-responders to anti-TNF

Current NICE guidelines [25] state that rituximab should be used

a. with methotrexate
b. in patients who have had an inadequate response to or intolerance of other DMARDs, including treatment with at least one anti-TNF therapy.
c. by physicians specialising in rheumatoid arthritis

It should be continued only if patients show an improvement in disease activity of 1.2 points or more. Repeat courses should be given with methotrexate and no more than 6 monthly.

This raises several questions:

i. Can rituximab be given without other DMARDs, or with alternatives to methotrexate?
ii. Should the eligibility and response criteria be modified?
iii. Should the suggested frequency of repeat infusions be modified?

i. Can rituximab be given without other DMARDs, or with alternatives to methotrexate?

The initial pivotal trial [26] included cyclophosphamide or methotrexate as the concomitant treatment. Although this was the initial open label trial, little difference existed between those treated with methotrexate and rituximab and those treated with cyclophosphamide and rituximab. In this trial, rituximab was also used as monotherapy with good efficacy, but this did not achieve significance versus placebo due to the small numbers in each group. The percentage figures for efficacy at 24 weeks are summarised in the table below.

Strategy	% achieving ACR20	% achieving ACR50	% achieving ACR70
Methotrexate	38	23	5
Rituximab alone	65	33	15
Cyclophosphamide and rituximab	76	41	15
Methotrexate and rituximab	73	43	23

Table 1. Efficacy of rituximab when used with a variety of other concomitant medications [19]

Recent data has suggested the possible role for leflunomide in patients intolerant of methotrexate [27,28]. There is very little data available regarding the combination of rituximab with other biologic therapies. In a small study with only 18 patients [29], patients were treated with etanercept and rituximab with good efficacy and no apparent significant increase in side effects with the etanercept discontinued a week before, and recommenced a week after the infusions. However, combination of other biologics has been associated with increased incidence of side effects, particularly infections, without increase in efficacy and therefore this area requires further research before any recommendation can be made [30].

ii. Should the eligibility and response criteria be modified?

All rituximab studies have enrolled patients with active RA. Some studies have only included those who have previously trialled anti-TNF therapy, whilst others have enrolled patients who have not had previous biologic therapy, with others including both groups of patients. The eligibility criteria for the major rituximab studies are similar: a swollen and tender joint count of equal to or more than 8 joints out of 68, an ESR of $\geq$ 28, and a CRP $\geq$ 1.5mg/dl. The Edwards et al trial stipulated that patients must be rheumatoid factor positive [26]. Other studies have not used this as an inclusion criterion but have only had small numbers of rheumatoid factor negative (seronegative) patients included.

Evidence suggests that seronegative patients do not respond as well to rituximab as patients who are rheumatoid factor positive (seropositive); however there may be some benefit in seronegative patients (see Table 10). One study failed to show significant response compared with placebo – but this study had 52% of patients achieved an ACR

20 on placebo [16]. Another study showed significant response in both groups but less in seronegative than seropositive patients (ACR 20 of 41% in seronegative and 54% in seropositive) [17].

Patients	Rituximab/ placebo	ACR 20 on Rituximab %	ACR20 on placebo %	P value	Reference number
RF pos %	79/79	54	19	<0.001	[10]
RF neg %	21/21	41	12	<0.001	[10]
RF pos	128/128	54	28	<0.003	[9]
RF neg	63/21	48	52	NR	[9]

Table 10. The responses of rheumatoid factor positive and negative RA patients to rituximab in two of the pivotal trials.

Preliminary data have shown that seropositivity to anti-CCP antibodies behaves in a similar fashion to seropositivity to RF [31], with greater responses in patients who are anti-CCP antibody positive than negative. Patients who convert to being seronegative for RF after their first infusion of rituximab appear to have a similar response as those who remain seropositive after their first infusion [32].

The BSR recommends that Rituximab should be given in patients with active rheumatoid arthritis who have failed biologics, or who are intolerant, or have contra-indication, to anti-TNF therapy. It should be borne in mind that patients who are rheumatoid factor positive or anti-CCP positive are more likely to respond to rituximab than patients who are negative for these antibodies.

The degree of EULAR responses in the pivotal trials show that a response of at least 1.2 DAS28 points is to be expected. The BSR recommends the use of at least a moderate EULAR response as the criterion for considering further treatments, for consistency with the BSR's recommendations for anti-TNF response criteria [33], and because EULAR response criteria are validated, whereas a DAS28 decrease of 1.2 irrespective of baseline DAS28 is not.

A delay of the assessment of response to 16 weeks should avoid the effect of the methylprednisolone infusion given with the rituximab, which is thought to last up to 8 weeks.

In a small study, patients who did not respond initially to rituximab also did not respond to further infusions [34]. In another small study, delaying the second treatment predicted a flare of disease, and gave a similar or enhanced secondary response [35]. An open label study looking at re-treatment has shown that a fixed re-treatment at 24 weeks and treating when a flare occurs have similar outcomes [36]. Data from Switzerland [37] suggests that the median duration of response in 83 RA patients was 12.7 months (inter-quartile range 9.4,22.3). There was some evidence that the efficacy of repeat infusions is cumulative. This was predicted by a good response to the first infusion.

The BSR recommends that RA arthritis patients on rituximab should be assessed for response at an interval of no less than 16 weeks. Patients who do not show at least a moderate EULAR response to the first treatment course should not be considered for re-treatment.

iii. Should the suggested frequency of repeat infusions be modified?

In an open follow up study in patients having more than one dose of rituximab [37] the interval between dosing was stable at 33 weeks (SD 10 weeks) in responders to the first dose. This was not different when stratified by anti-TNF therapy and non anti-TNF therapy exposed patients. The BSR recommends that re-treatment with rituximab in RA should be considered when initial treatment response of at least a moderate EULAR response has been lost. The frequency of infusion should be no less than 24 weeks.

Abatacept in RA non-responders to anti-TNF

Abatacept is a selective T cell co-stimulation modulator that blocks the CD80:CD28 or CD86:CD28 co-stimulatory signal that is required for full T cell activation. Abatacept is a fusion protein comprising the extracellular domain of human CTLA4Ig and a fragment of the Fc domain of human IgG1, produced by recombinant DNA technology in Chinese hamster ovary cells. CTLA4Ig has a greater affinity for CD80 or CD86 than it does for CD28, and as such it preferentially binds to these receptors, thus preventing normal co-stimulation via CD28. Abatacept is licensed for use in the UK in combination with Methotrexate for the treatment of moderate to severe rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other DMARDs including at least one TNF inhibitor.

NICE Technology Appraisal Guidance 141 [38] has not recommended abatacept for the treatment of patients with RA, on grounds of not being a cost effective use of NHS resources. This includes those in whom rituximab has failed or in whom rituximab is contra-indicated or not tolerated. The Summary of Product Characteristics does not recommend abatacept in combination with TNF blocking drugs because of an increase in overall and serious infections.

RA patients who have failed to tolerate or respond to TNF inhibitors have a limited therapeutic choice, between

- rituximab; or
- a return to non-biologic DMARDs alone or in combination;
- or corticosteroids.

RA patients who do not respond to therapies have a well documented poor outcome with respect to damage within the musculoskeletal system, and effects on cardiovascular and bone health, overall quality of life and life expectancy. In this context any treatment with proven efficacy is attractive, not least abatacept given the unique mechanism of action.

NICE did not dispute the fact that abatacept was efficacious in the treatment of RA. In order to move this debate on, it would therefore be important to focus on the following issues:

i. Is there any new evidence to show that the efficacy of abatacept may have been under-estimated in the treatment of RA?

ii. Is there any new evidence to show that abatacept might have advantages over other comparators (conventional DMARDs, anti-TNF therapies or rituximab) in treating all RA, or sub-groups of disease?

i. Evidence that the efficacy of Abatacept may have been under-estimated

1. Randomised, double blind, placebo controlled dose ranging add-on to methotrexate non-responders study [39-41].

   339 patients with active RA despite methotrexate were randomised to placebo (with methotrexate), abatacept 2mg/kg or 10 mg/kg (days 1, 15, 30 then every 30 days) up to 1 year, then all switched to open label abatacept 10mg/kg every 30 days. Significant improvement was seen at 1 year in ACR 20/50/70, L-DAS, HAQ and SF-36 (6 months data only) in 10mg/kg but not 2mg/kg compared with placebo. At 5 years, abatacept remained well tolerated and provided sustained benefits, with a higher proportion of patients achieving L-DAS and DAS-R at year 5 than year 1.

2. 'AIM': Randomised, double blind, placebo controlled add-on to MTX non-responders study [42-48].

   652 patients with active disease despite 15 mg or more of methotrexate were randomised to continue methotrexate and either have placebo, or abatacept 10 mg/kg (days 1, 15, 30 then every 30 days), then all placebo patients were switched to abatacept 10mg/kg.

   Significant improvement was seen in ACR 20/50/70, L-DAS, DAS-R, HAQ and radiographic outcome at 1 year versus placebo and sustained improvements at year 2 and 3 in all outcomes with suggestion of further incremental benefit on L-DAS, DAS-R and radiographic outcome, whereas the ACR20/50/70 had a plateau effect at year 2, and HAQ / SF-36 outcome had a plateau effect at year 1, with maintained responses at year 2.

3. 'ATTAIN': Randomised, double blind, placebo controlled switch to Abatacept in anti-TNF non-responders study [45,46,48-52]

   391 patients with active RA despite DMARDs and either current or prior anti-TNF (infliximab and etanercept) were included. DMARDS (75% on methotrexate) and oral prednisolone up to 10mg (70%) were continued but the dose was stable for 3 months. Anti-TNF therapy was stopped (former users 62%, current users 38%, washout etanercept 28 days and infliximab 60 days). Abatacept 10 mg/kg or placebo was given on days 1, 15, 30 then every 28 days, then all placebo patients were switched to abatacept 10mg/kg on day 141 ABA. A significant improvement was seen in ACR 20/50/70, L-DAS, DAS-R, HAQ and all SF-36 domains at 6 months. In the long term extension phase at year 2 and 3 incremental increases were seen in ACR 20/50/70, L-DAS, DAS-R, whereas no further improvements were observed in SF-36 and HAQ after 6 months. Placebo treated patients in the first 6 months showed similar benefit when switched to abatacept. The numbers of patients with greater L-DAS or DAS-R were higher if previously they had failed one anti-TNF agent as opposed to 2 anti-TNF agents. No difference in outcome was seen if the reason for stopping anti-TNF therapy was primary versus secondary non-response.

In conclusion, three large cohorts of patients have all shown that the maximum benefit from abatacept may be seen after the first year of treatment. The BSR recommends that abatacept should be available to RA patients who have failed to respond to other biological agents. Health economic analyses of abatacept should take into account the increase in efficacy that takes place after the first year of treatment.

ii. Evidence of advantages of abatacept over other comparators

Rituximab may be more effective in seropositive RA than seronegative disease. The only data the BSRBG have been able to find for this on abatacept is that presented by Bristol-Myers Squibb to the US Food and Drugs Administration. This covers efficacy in seronegative patients compared to seropositive patients in AIM (20% RF negative) and ATTAIN (27% RF negative) (see page 57 (AIM) and page 74 (ATTAIN)) [52]. In summary, ACR response rates were greater for abatacept than placebo in both seropositive and seronegative patients in both studies, with no obvious differences between the groups.

The ATTAIN study extension has shown that there is no difference in efficacy for patients demonstrating primary or secondary non-response on anti-TNF therapy, in contrast to the data for a second anti-TNF agent which may not be as effective under in primary compared with secondary non-responders.

If NICE eventually approves abatacept, it is likely that the drug would be used after the failure of rituximab in the UK. Genovese et al [49] report safety outcome in 185 patients with active RA despite rituximab therapy, who were then treated with another biologic drug over a median follow up period of 11 months. Of these 150 received an anti-TNF drug and 25 received abatacept. At the time of commencing the post-Rituximab biologic the majority had a CD19 count below the lower limit of normal. There is no report of an increase in the incidence of serious infections during post-Rituximab biologic exposure compared to during-Rituximab treatment. Also there were no opportunistic or fatal infections in the post-Rituximab biologic period. This is reassuring for the group of patients most likely to gain access to abatacept in the UK.

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The British Society for Rheumatology Biologics Register

Updated analysis on sequential use of anti-TNF therapies in patients with rheumatoid arthritis

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Table of Contents

1. The British Society for Rheumatology Biologics Register – Background and Recruitment Update

The British Society for Rheumatology Biologics Register (BSRBR) was launched in October 2001. The primary aim of this study was to investigate the long-term outcome of patients with RA treated with biologic agents with particular reference to safety. The study was organised under the auspices of the British Society for Rheumatology and based at the Arthritis Research Campaign Epidemiology Unit (arc EU) at The University of Manchester. Funding for this study comes from the pharmaceutical companies that market anti-TNF agents and other biologics in the UK to the BSR. To date these companies have included Amgen, Abbott Laboratories, Biovitrum, Roche Schering-Plough, and Wyeth. Each company has a separate contract with the BSR, which in turn has awarded the arc Epidemiology Unit a research grant for the running of the study. In return, The University of Manchester provides the pharmaceutical companies with a "pharmacovigilance service" which includes expedited reporting of serious adverse events and 6 monthly SAE incidence rate comparisons and periodic safety update reports (PSURs) according to an agreed template. Decisions on analyses and publications for academic purposes rest solely with the University of Manchester and the BSR.

The register runs in parallel with other European registries, in particular registers established in Germany and Sweden, which are funded by similar routes and are collecting the same core data. Representatives from these registers meet on an annual basis to discuss progress of the registers as well as issues related to the collection and analysis of data.

Sample Size and Patient Recruitment

The original sample size calculation for the BSRBR was based on the ability to detect a two-fold increase in lymphoma. This equated to 20000 person years in both a treated and untreated cohort. For ease, this was equated to a sample size of ~4,000 patients with a follow-up of 5 years each, for each of the three currently available NICE approved anti-TNF drugs (etanercept, infliximab and adalimumab) and a

similarly sized DMARD treated control group. Patients on biologics have been recruited from 251 hospitals across the UK. The majority have very active disease (DAS28 > 5.1) which has been resistant to at least 2 DMARDS, in accordance with the current national guidelines on the use of these agents (1). In 2005, the target of 4000 etanercept treated patients was reached and recruitment to this cohort was closed. The last of 4000 infliximab treated patients was recruited in early 2007 and recruitment to the adalimumab cohort came to an end towards the end of 2008. The register has also recruited a parallel cohort of biologic-naïve patients with active disease (guide DAS28 >4.2) who are receiving traditional disease modifying therapy (DMARDs). Recruitment to this cohort, also set at a target of 4000 patients, was completed in March 2009.

Study Design and Patient Follow-up

All patients (anti-TNF treated and DMARD controls) have six-monthly questionnaires completed by the rheumatologist or rheumatology nurse specialist for the first 3 years of the study and then annual questionnaires thereafter. In addition, patients completed a diary recording all hospitalisations and other adverse events six-monthly for 3 years. All patients are also "flagged" with the national NHS Information Centre, which provides ongoing information on all patients who die or develop a malignancy within the UK. Despite this intensive program, the follow-up rates have been excellent, with 90% of available hospital follow-up returned to the arc EU. Patient response rates have also been very good, with 75% of all diaries returned. Regular feedback to patients and health care professionals via newsletters and results presented at national rheumatology meetings has helped to maintain the momentum of this study.

2. Measuring Treatment Effectiveness using Data from the BSR Biologics Register

The BSRBR was primarily set up to capture long-term outcomes with reference to safety in patients starting anti-TNF and other biologic therapies. However, disease activity and severity is one of the most important confounders in the relationship

between treatment and outcome and therefore, in addition to details of adverse events, regular collection of disease activity markers have also been collected. These have primarily included the 28-joint count disease activity score (DAS28), the Health Assessment Questionnaire (HAQ), the Short-Form 36 (SF-36) and most recently, the addition of the Euroqol-5D (in patients registered since 2006). The measures are collected at the start of therapy and then at 6-monthly intervals thereafter for three years. These scores are not necessarily collected at the time that patients stop their therapy and/or start a subsequent biologic therapy.

With these data, we have been able to determine the proportion of patients who respond to their first anti-TNF therapy with much accuracy and have also been able to look at predictors (clinical and genetic) of this response (2-10).

Analysis of response to a second or further biologic agent (with the exception of rituximab) has proven more difficult. However, we do collect the dates of treatment starts and stops as well as the dates of the disease activity/disability scores and so have had the opportunity among the large numbers of patients enrolled in this study (n=19,198), to do subset analyses of those patients where these 2 events do correspond (drug start/stop and measurement of disease activity) albeit in smaller numbers. Our data analyses have focused primarily on the HAQ score, as this is the outcome measure can be mapped to the EQ5D and thus QALY's (11;12) and so can be used in health economic analyses. This approach is not without its limitations. The most important of these is the limitations of using HAQ as a measure of treatment response in patients with long-standing RA (13;14). In early RA, HAQ has been shown to correlate closely with disease activity whereas, in late disease; the score may reflect permanent joint damage and so have an irreversible component. As a result, patients can have a significant improvement in pain and swelling and therefore quality of life, yet this may not be reflected in large changes in their HAQ scores. Indeed, in the original clinical trials of anti-TNF therapies in patients with long-standing RA (mean 12 years), improvements in the range of 0.3 HAQ units were seen (after adjusting for a placebo effect), which is similar to that seen with a first anti-TNF therapy in the BSRBR.

We have not included an analysis of rituximab in this report. The BSRBR has recently added the collection of patients starting rituximab to its study protocol. However, this collection only started in May 2008 and so is limited in size and follow-up. Therefore, it has not yet been evaluated.

3. The BSR Biologics Register – Published Data on the Sequential Use of Anti-TNF Therapies

To July 2009, the BSRBR had published 5 papers looking specifically at treatment effectiveness in RA.

1. Hyrich KL, Symmons DP, Watson KD, Silman AJ; British Society for Rheumatology Biologics Register. **Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register.** Arthritis Rheum. 2006 Jun;54(6):1786-94.

2. Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. **Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register.** Rheumatology (Oxford). 2006 Dec;45(12):1558-65.

3. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ; British Society for Rheumatology Biologics Register. **Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study.** Arthritis Rheum. 2007 Jan;56(1):13-20.

4. Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP; BSR Biologics Register. **Effects of switching between anti-TNF therapies on HAQ response in**

patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008 Jul;47(7):1000-5.

5. Brennan A, Bansback N, Nixon R, Madan J, Harrison M, Watson K, Symmons D. **Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry.** Rheumatology (Oxford). 2007 Aug;46(8):1345-54.

The first 2 papers deal with predictors of response to the first course of anti-TNF therapy. The next 2 papers present analyses of sequential use of anti-TNF therapies. The third paper above included data to April 2005 and the fourth paper to July 2006. The final paper (Brennan et al) presents an analysis of the cost-effectiveness of anti-TNF therapies, using data from the BSRBR. The purpose of this current report is to present an updated analysis on the sequential use of anti-TNF therapies (publications 3 and 4 above) with data current to 2 July 2009. **This report is not meant to be read in isolation but to be read along side the original publications (attached in Appendices), with the accompanying statistical methodology and discussion.**

3.1. Outcomes after switching from one anti-TNF agent to a second anti-TNF agent in patients with rheumatoid arthritis – Updated Analysis

The primary aim of this analysis was to study the risk of recurrent inefficacy and adverse events in patients who were switched to a second course of anti-TNF therapy. Our original publication can be found in Appendix 1.

Inefficacy and adverse events were determined by the treating physician and the outcome was drug discontinuation for the listed reason for stopping treatment. The analysis, stratified according to the reason the patient stopped the first drug, compared the rate of stopping a second drug for either inefficacy or adverse events to the rate of stopping the first drug for either inefficacy or an adverse event in the whole cohort.

Our original publication included data up until April 2005. This included a total of 6739 patients (856 (13%) received a second anti-TNF agent). This updated analysis includes an additional four years of data; a total of 12626 patients (2876 (23%) patients with sequential anti-TNF use). Compared to our original analysis, the follow-up per person is significantly longer (max 96 months versus 61 months). Given this longer follow-up time, we have seen a higher proportion of patients who have now discontinued their first anti-TNF agent (51% versus 35%). However, as we have previously observed, the proportion of patients who stop for either an adverse event or inefficacy remain the same (Table 3.1-1).

Table 3.1-1 Details of treatment with the first anti-TNF agent (Data up to 2 July 2009)

	Total cohort	Adalimumab	Etanercept	Infliximab
Total starts, no.	12,626	4,120	4,393	4,113
Still taking agent at 2/7/2009, n (%)	6,167 (49)	2,293 (56)	2,314 (53)	1,560 (38)
Mean/maximum duration of therapy, months*	28/96	22/72	32/96	29/84
Mean/maximum duration of follow-up, months	35/96	25/72	38/96	41/88
Discontinuations, n (%)	6,459 (51)	1,827 (44)	2,079 (47)	2,553 (62)
Stopped first agent for inefficacy, n (%)	2,544 (20)	786 (19)	787 (18)	971 (24)
Switched to second agent, n (% of those who stopped)	1881 (74)	530 (67)	575 (73)	776 (80)
Stopped first agent for adverse event, n (%)	2,573 (20)	728 (18)	905 (21)	940 (23)
Switched to second agent, n (% of those who stopped).	995 (39)	232 (32)	265 (29)	498 (53)

* First anti-TNF only

Table 3.1-2 shows the differences in baseline characteristics among the entire cohort (n=12626) and among those subgroups of patients who discontinued treatment, based on whether or not they commenced a second anti-TNF agent. Overall, there were no significant differences between the groups.

Table 3.1-2 Baseline characteristics of the entire cohort and the groups which stopped the first biologic agent, according to reason for stopping and whether or not a second agent was started

	Total cohort (all starts)	Stopped first agent for inefficacy		Stopped first agent for adverse event	
		No switch	Switch	No switch	Switch
No. of patients	12,626	661	1,881	1,577	995
Age, mean ± SD years	56 ± 12	58 ± 12	54 ± 12	60 ± 11	55 ± 12
Female sex, no. (%)	9,622 (76)	521 (79)	1,508 (80)	1,174 (74)	807 (81)
Disease duration, mean ± SD years	13 ± 10	13 ± 10	12 ± 9	15 ± 10	14 ± 10
DAS28, mean ± SD	6.6 ± 1.0	6.6 ± 1.0	6.7 ± 1.0	6.6 ± 1.0	6.7 ± 1.0
HAQ, mean ± SD score	2.0 ± 0.6	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5

Table 3.1-3 shows the patterns for switching between anti-TNF therapies. More patients switched from than to infliximab. This may in part be explained by the fact that infliximab was the first available anti-TNF therapy, with etanercept use increasing significantly after 2003 and adalimumab after 2004. However, patients whose first drug was etanercept or adalimumab were more likely to switch to the alternative injectable medication rather than infliximab.

Table 3.1-3 Pattern of anti-TNF switches, based on the reason for discontinuation of the first anti-TNF agent*

	Second anti-TNF agent			
First anti-TNF agent	Etanercept	Infliximab	Adalimumab	Total
Etanercept				
Reason for stopping				
Inefficacy	NA	163	412	575
Adverse event	NA	57	208	265
Infliximab				
Reason for stopping				
Inefficacy	481	NA	295	776
Adverse event	332	NA	166	498
Adalimumab				
Reason for stopping				
Inefficacy	451	79	NA	530
Adverse event	206	26	NA	232
Total	1470	325	1081	2876

* Values are the number of patients.

Table 3.1-4 shows the proportion of patients stopping their second anti-TNF therapy, with reason. Again, the total period of observation has increased and the proportion of patients who have now stopped their second anti-TNF has also increased. The mean and maximum observed duration of treatment with a second anti-TNF agent are 18 and 64 months respectively (In April 2005 the equivalent times were 6 and 32 months respectively). We observed a similar pattern to that observed in April 2005, whereby those patients who stop a first anti-TNF for inefficacy are more likely to stop a second drug for inefficacy, but no more likely to stop for an adverse event (compared to the risk on their first anti-TNF) (Table 3.1-5 and Figures 1a and 1b). The opposite was true for adverse events, where a person was twice as likely to stop a second drug for an adverse event (compared to the overall risk of stopping the first drug for an adverse event) if their first drug was also stopped for an adverse event. We have now observed that patients who switched for an adverse event were slightly less likely to stop a second drug for inefficacy than the whole cohort on their first anti-TNF (HR 0.86 (95% CI 0.75, 0.98)).

Table 3.1-4 Outcomes of treatment with the second biologic agent*

	Outcome with second biologic agent		
Reason for switch	**Still taking agent at 2/7/09**	**Stopped for inefficacy**	**Stopped for AE**
Inefficacy (n = 1,881)	1138 (60)	482 (26)	261 (14)
AE (n = 995)	541 (54)	174 (17)	280 (28)
Total switches (n = 2,876)	1630 (57)	656 (23)	541 (19)

*values are number (%) of patients; AE = adverse event

Table 3.1-5 Risk of Stopping Second Anti-TNF Based on Reason for Switching Therapy

	Hazard Ratio (95% CI)
Stopped first drug for inefficacy	
Risk of Stopping Second Drug for Inefficacy	1.71 (1.55, 1.90)
Risk of Stopping Second Drug for Adverse Event	1.03 (0.89, 1.19)
Stopped first drug for adverse event	
Risk of Stopping Second Drug for Inefficacy	0.86 (0.75, 0.98)
Risk of Stopping Second Drug for Adverse Event	1.96 (1.76, 2.18)

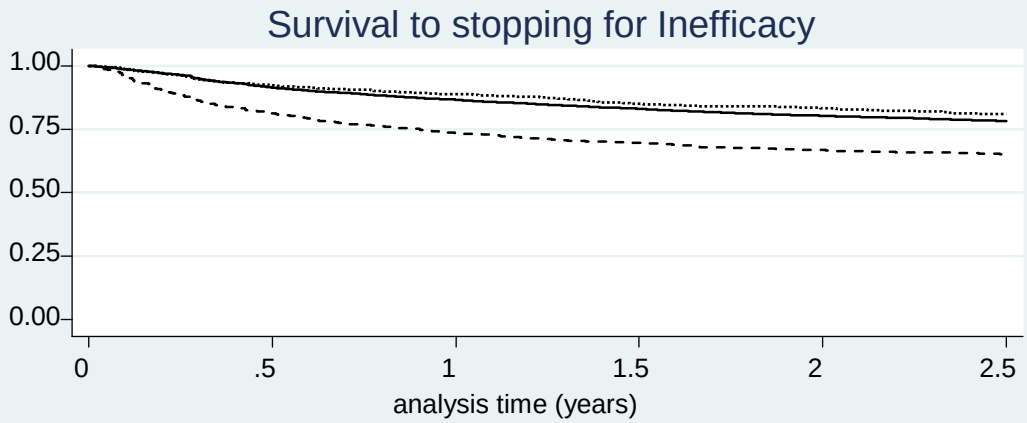

Figure 1a. Drug discontinuation due to inefficacy. Continuation rates are shown for patients receiving their first course of therapy (solid line) as compared with the second course in patients who discontinued their first course due to inefficacy (dashed line) and those who discontinued their first course due to an adverse event (dotted line).

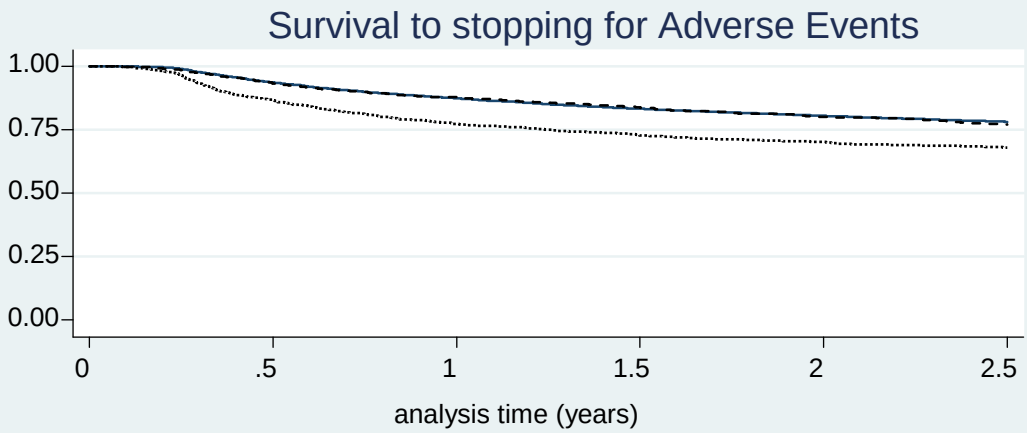

Figure 1b. Drug discontinuation due to adverse events. Continuation rates are shown for patients receiving their first course of therapy (solid line) as compared with the second course in patients who discontinued their first course due to inefficacy (dashed line) and those who discontinued their first course due to an adverse event (dotted line).

3.2. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug – Updated Analysis

One of the greatest challenges in using observational data to measure treatment effectiveness is that disease activity assessments submitted to the register may not always coincide with treatment starts and stops. However, the size of the BSRBR permits us to identify subgroups of patients where a measure of disease activity has been captured near to a time of treatment change. Therefore, this second switching analysis, aimed to measure the effect of switching anti-TNF therapy on HAQ scores over a 12 month period, was performed in a subset of patients who had HAQ scores recorded within 3 months of non-response to their first anti-TNF therapy (defined as stopping due to inefficacy or a EULAR non-response by DAS28 within the first 12 months of treatment) and a second HAQ score measured 12 months later. The original publication can be found in Appendix 2.

Patients who were classified as non-responders were divided into three groups based on subsequent therapy over the next 12 months and their change in HAQ score over this 12 month period was measured.

Group 1—'Stoppers': discontinued anti-TNF therapy within the first 12 months and did not start a subsequent anti-TNF agent or other biologic drug during the next 12 months.

Group 2—'Stayers': continued on their original anti-TNF agent despite being classified as a non-responder and remained on therapy until at least within 90 days of the final HAQ measurement (i.e. for a minimum of further 9 months).

Group 3—'Switchers': stopped their first anti-TNF therapy within the first 12 months of therapy for non-response but started a second anti-TNF therapy during the subsequent 12 months. To capture the full experience of patients who switched between anti-TNF therapies, Group 3 included all patients who started a second anti-TNF at any time during the next 12 months. As this group was quite varied (i.e. the

group may have included a proportion of patients who switched towards the end of this 12 month period), we also identified a subgroup of patients within Group 3 who switched early (within 90 days of being classified as a non-responder) and remained on the second anti-TNF therapy at least until within 90 days of the second HAQ measurement (**'Early Switchers**') to ensure at least 6 months treatment with the second anti-TNF therapy.

The original analysis was performed using data to July 2006 and included outcomes on 856 patients. This updated analysis (to July 2009), now includes 1345 patients. For 86% of patients, non-response was determined by 6 months, with the remaining 14% determined by 12 months. It is not known how many patients had primary non-response and what proportion may have had an original response and then had a secondary failure.

In total, there were 202 patients who discontinued their first anti-TNF and received no further anti-TNF therapy during the subsequent year (Stoppers), 609 patients who continued the drug for the duration of the next 12 months despite being classified as a non-responder (Stayers) and 534 patients who discontinued their first anti-TNF and started a second anti-TNF within the next 12 months (Switchers). Of these, 279 fulfilled the criteria as an early switcher (Early Switchers). Characteristics of the patients at the start of their first anti-TNF therapy are shown in Table 3.2-1. Details of anti-TNF treatments prescribed during the first and second course are presented in Table 3.2-2.

Table 3.2-1 Characteristics of Patients at Start of First Anti-TNF Therapy*

	Stoppers (202)	Stayers (609)	All Switchers (534)	Early Switchers (279)
Age, years†	61 (53, 68)	58 (50, 66)	58 (50, 65)	58 (50, 65)
Female, n (%)	158 (78.2)	491 (80.6)	430 (80.5)	219 (78.5)
Disease duration, years†	12 (7, 19)	12 (6, 19)	10 (5, 17)	10 (5, 17)
DAS28†	6.5 (5.9, 7.3)	6.2 (5.5, 6.8)	6.7 (6.0, 7.3)	6.6 (6.0, 7.3)
Previous DMARDS	4 (3, 5)	4 (3, 5)	4 (3, 5)	4 (3, 5)
DMARD, n (%)	117 (57.9)	409 (67.2)	353 (66.1)	191 (68.5)
MTX, n (%)	96 (47.5)	323 (53.0)	270 (50.6)	147 (52.7)
Oral Steroid, n (%)	105 (52.0)	279 (45.8)	239 (44.8)	122 (43.7)
NSAID, n (%)	114 (56.4)	366 (60.1)	30 (61.8)	177 (63.4)

*All results Median IQR unless stated, † Difference between Stoppers, Stayers and All Switchers significant at $p<0.05$.

Table 3.2-2 Proportion of Patients Starting Each Anti-TNF Therapy (First and Second Course)

Anti-TNF Agent	First Course (n=1345)	Second Course (n=534)
Etanercept	35	51
Infliximab	31	17
Adalimumab	34	32

Table 3.2-3 shows the presenting HAQ score, HAQ score at first failure, HAQ score 12 months following first failure and the change in HAQ score according to the therapy received during the 12 months following non-response. A negative change in HAQ score indicates an improvement and a positive score indicates deterioration. Compared to patients who stopped their anti-TNF and received no further biologic therapy over the next 12 months, patients who stayed on the drug or stopped and then switched to a second anti-TNF tended towards slightly lower HAQ scores at the start of their first anti-TNF therapy and also had a greater improvement in their HAQ score with their first anti-TNF therapy despite being classified as non-responders (greatest

improvement in Stayers). Over the course of the next 12 months, the greatest improvement in HAQ score was seen in patients who switched therapy. This was noted particularly in those patients who switched the drug early in the course and remained on the therapy for at least 6 months. We also observed a greater proportion of patients who achieved a minimally clinical important difference in their HAQ score (0.22 units) in the Switchers subgroup.

It is interesting to note that patients who continued on their anti-TNF therapy despite being classified as a non-responder continued to show improvement in their HAQ scores over the course of the next 12 months. It is not known whether there were additional changes to therapy, such as the use of corticosteroids or changes to background DMARD therapy (i.e. new therapy or increase in dose of existing therapy).

Table 3.2-3 HAQ Scores and Change in HAQ Scores

Group	HAQ at start of first anti-TNF, mean (SD)	HAQ at first failure, mean (SD)	Unadjusted mean change in HAQ with first anti-TNF (95% CI)	HAQ 12 months after first failure, mean (SD)	Adjusted mean change in HAQ over 12 months following first failure, (95% CI)	n(%) with MCID 12 months following first failure*
Stoppers (202)	2.12 (0.52)	2.1 (0.54)	-0.02 (-0.07, 0.03)	2.1 (0.58)	Reference	51 (25)
Stayers (609)	2.04 (0.56)	1.9 (0.62)	-0.13 (-0.16,-0.10)	1.84 (0.61)	-0.10 (-0.17,-0.03)	193 (32)
All Switchers (534)	2.08 (0.52)	2.0 (0.56)	-0.08 (-0.11,-0.05)	1.89 (0.64)	-0.11 (-0.18,-0.05)	187 (35)
Early switchers (279)	2.06 (0.54)	1.94 (0.60)	-0.12 (-0.17,-0.07)	1.80 (0.69)	-0.17 (-0.24,-0.09)	106 (38)

* Defined as an improvement of at least 0.22 HAQ units (15); MCID – minimally clinically important difference

4. Changing Pattern of UK Anti-TNF Prescribing 2001-2008

As an exploratory analysis in response to clinical impressions that anti-TNF therapy may be being used earlier in the disease course and so in patients with milder disease than the original recipients, we have undertaken a descriptive analysis of the pattern of baseline disease characteristics at the start of anti-TNF therapy over the course of the study and the early changes in disease activity. This analysis was presented originally at the British Society of Rheumatology AGM in 2009 (7) and is updated in this report (data to July 2009).

The overall trend was for the earlier use of anti-TNF therapy in patients with RA (Table 4-1). There were also significant trends towards a decrease in disease activity and disability at the start of therapy over the course of the study. Corresponding to these changes, we also observed a higher proportion of moderate and good EULAR responders as well as an increasing proportion of patients who achieved disease remission at both 6 months and one year (Table 4-2 and Table 4-3). The overall intensity of the response (good versus moderate) has also improved year on year. Despite these improvements in disease activity, the mean improvement in HAQ score has remained constant over the course of the study, at a mean of around 0.30 units (Table 4-4).

Table 4-1 Baseline Characteristics of Anti-TNF Treated Patients by Year of First Treatment Start

	2,001	2002	2003	2004	2005	2006	2007	2008	p for trend
n	129	1,306	3,167	3,317	1,654	1,164	865	486	
Age	55 (44, 63)	55 (46, 62)	57 (48, 65)	58 (49, 65)	57 (49, 65)	58 (48, 65)	57 (48, 65)	58 (48, 66)	<0.001
Female	100 (78)	994 (76)	2427 (77)	2516 (76)	1245 (75)	886 (76)	658 (76)	389 (80)	0.624
Disease duration	13 (8, 20)	12 (7, 19)	12 (7, 19)	11 (6, 19)	11 (5, 18)	10 (5, 17)	9 (4, 17)	9 (4, 17)	<0.001
DAS28	6.8 (6.1, 7.6)	6.8 (6.1, 7.4)	6.7 (6.0, 7.4)	6.6 (5.9, 7.3)	6.5 (5.8, 7.2)	6.4 (5.7, 7.1)	6.4 (5.7, 7.1)	6.4 (5.7, 7.0)	<0.001
HAQ	2.4 (1.9, 2.6)	2.3 (1.9, 2.5)	2.1 (1.8, 205)	2.1 (1.8, 2.5)	2.0 (1.6, 2.4)	2.0 (1.6, 2.4)	1.9 (1.5, 2.4)	2.0 (1.5, 2.3)	<0.001
Previous number of DMARDs	5 (4, 6)	4 (3, 6)	4 (3, 6)	4 (3, 5)	3 (2, 5)	3 (3, 4)	3 (3, 4)	3 (2, 4)	<0.001
Disease duration < 5 years	11 (9)	169 (13)	449 (14)	615 (19)	370 (23)	275 (24)	233 (27)	140 (29)	<0.001
Disease duration < 2 years	3 (2)	57 (4)	162 (5)	278 (8)	161 (10)	132 (11)	122 (14)	62 (13)	<0.001

Table 4-2 Change in DAS28 and EULAR Response at 6 months

Start Year	Mean Change in DAS28 (SD)	% with no response	% with moderate response	% with good response	% in remission at 6 months
2001	-2.11 (1.51)	25.3	56.6	18.2	7.8
2002	-2.19 (1.56)	22.9	56.1	21.0	9.3
2003	-2.13 (1.53)	23.3	56.6	20.1	9.0
2004	-2.32 (1.51)	19.1	56.3	24.7	12.7
2005	-2.32 (1.55)	20.1	53.4	26.5	14.7
2006	-2.22 (1.63)	22.4	49.1	28.5	14.7
2007	-2.23 (1.54)	20.2	51.2	28.6	15.8
2008	-2.21 (1.57)	22.4	48.4	29.2	16.9
p	0.064	0.117*		<0.001†	<0.001

* p value for any responder versus non responder in each consecutive year
† p value for odds of being in higher response category in each consecutive year

Table 4-3 Change in DAS28 and EULAR Response at 12 months

Start Year	Mean Change in DAS28 (SD)	% with no response	% with moderate response	% with good response	% in remission at 12 months
2001	-1.96 (1.35)	30.4	53.2	16.5	7.8
2002	-2.33 (1.59)	22.5	55.6	21.9	9.3
2003	-2.32 (1.62)	21.5	54.0	24.5	9.0
2004	-2.39 (1.54)	17.5	56.1	26.4	12.7
2005	-2.44 (1.61)	18.9	51.0	30.1	14.7
2006	-2.33 (1.71)	21.4	46.5	32.1	14.7
2007	-2.42 (1.56)	17.3	47.2	35.5	15.8
2008	-2.29 (1.69)	20.9	49.4	29.7	16.9
p	p=0.116	*0.018		<0.001†	<0.001

* p value for any responder versus non responder in each consecutive year
† p value for odds of being in higher response category in each consecutive year

Table 4-4 Change in HAQ score by year of anti-TNF start

Start Year	Change in HAQ after 6 months	Change in HAQ after 12 months
2001	-0.25 (0.70)	-0.29 (0.74)
2002	-0.32 (0.48)	-0.33 (0.50)
2003	-0.31 (0.50)	-0.32 (0.51)
2004	-0.31 (0.51)	-0.32 (0.53)
2005	-0.33 (0.52)	-0.34 (0.54)
2006	-0.33 (0.56)	-0.35 (0.55)
2007	-0.31 (0.56)	-0.33 (0.56)
2008	-0.30 (0.52)	-0.35 (0.56)
p	0.735	0.216

Subsequent to this we re-explored the 2 switching analysis we had undertaken, stratifying analysis by treatment year. However, the analyses, particularly in later years, became significantly restricted by low patient numbers with sufficient follow-up to observe outcomes on a second agent. Small numbers prevented a year-on-year analysis of the change in HAQ score following failure of first anti-TNF, as a minimum of 18 months of observation were required, therefore leaving very few patient in the latter years of study. Therefore, we elected to not undertake a stratified analysis of change in HAQ following failure of a first anti-TNF (Table 4-5).

Table 4-5 Number of Starts per Year in Analysis of Change in HAQ Following Failure of a First Anti-TNF

Study Year	Stayers	Stoppers	All Switchers	Early Switchers	Total in Year
2001	15	4	4	1	**23**
2002	68	21	53	24	**142**
2003	204	63	150	76	**417**
2004	164	56	145	80	**365**
2005	86	29	93	55	**208**
2006	50	18	62	35	**130**
2007	22	11	25	8	**58**
2008	0	0	2	0	**2**
Total	**609**	**202**	**534**	**279**	**1,345**

Analysis of the survival of a second anti-TNF based on reason for the switch was undertaken on a year by year analysis. There was a trend towards a lower proportion of patients switching between anti-TNF therapies in the later years of the study. Overall, although small numbers prevented robust estimates in later years, the risks of stopping a second agent based on the reason for stopping the first did not differ from the overall analysis presented in Section 3.1 (Table 4-6).

Table 4-6 Year by year analysis of Anti-TNF Survival Based on Reasons for Switching

Start Year	Number of first starts in year	Stopped for inefficacy or adverse events by 02/07/09, n (% of those who started)	Switched following inefficacy or AE n (% of those who stopped)	Failed First Drug for Inefficacy			Failed first drug for adverse event		
				n	Risk of failing second for inefficacy HR (95% CI)	Risk of failing second for AE HR (95% CI)	n	Risk of failing second for inefficacy HR (95% CI)	Risk of failing second for AE HR (95% CI)
2001/2	2,191	955 (43.6)	647 (67.7)	396	1.56 (1.22, 2.01)	1.11 (0.82, 1.51)	251	0.73 (0.53, 1.01)	1.50 (1.15, 1.96)
2003	3,258	1491 (45.8)	848 (56.9)	552	1.56 (1.29, 1.89)	0.93 (0.71, 1.22)	296	0.91 (0.73, 1.13)	2.05 (1.71, 2.45)
2004	3,301	1300 (39.4)	680 (52.3)	452	1.97 (1.61, 2.40)	1.19 (0.90, 1.58)	228	0.77 (0.59, 1.01)	1.93 (1.56, 2.39)
2005	1,625	632 (38.9)	346 (54.7)	243	1.61 (1.22, 2.11)	0.83 (0.51, 1.36)	103	0.76 (0.51, 1.13)	2.20 (1.59, 3.10)
2006	1,153	448 (38.9)	229 (51.1)	153	1.62 (1.14, 2.31)	0.95 (0.53, 1.71)	76	0.69 (0.42, 1.15)	1.86 (1.18, 2.83)
2007	829	239 (28.8)	112 (46.9)	79	2.20 (1.30, 3.74)	0.80 (0.29, 2.26)	33	1.47 (0.74, 2.92)	2.86 (1.61, 5.09)
2008	269	52 (19.3)	14 (26.9)	6	Not analysed due to too few first and second starts		8	Not analysed due to too few first and second starts	

*** Each analysis is limited to those patients who started their first anti-TNF during the given study year.**

5. Improvements in Quality of Life

To date, our analyses have used either drug survival or changes in HAQ scores to explore the effects of switching on outcomes in patients receiving anti-TNF therapies for RA. However, neither of these outcomes can be directly used in health economic analysis. In mid-2006 the BSRBR added the Euro-Qol 5D (EQ-5D) to its data collection. However, for the interest of this current report, fewer than 190 patients in the analysis presented in Section 3.2 had a EQ-5D recorded and therefore, we subsequently mapped the HAQ scores observed in Section 3.2 (Table 3.2-3) to the EQ5D, using the technique described by Bansback et al (12). This technique has been shown to be valid in the BSRBR and other RA datasets (16;17) although there is a concern that this technique may underestimate changes in EQ5D over time (16;17). These results are presented in Table 5.1. Of note, the mean follow-up after failure of a first anti-TNF was 1 year and therefore, it is not unreasonable to view the EQ5D change over this 12 month period as representing the quality adjusted life years gained over this same period. This change (adjusted mean change in EQ5D in Early Switchers following failure of a first anti-TNF 0.08 (95% CI 0.04, 0.13) is small but in excess of what is considered a minimally important difference in EQ5D (18).

Table 5-1 Mapped EQ5D Scores and Change in Mapped EQ5D Scores

Group	Mean total follow-up, years (SD)	EQ5D at start of first anti-TNF, mean (SD)	EQ5D at first failure, mean (SD)	Mean time to first failure, years (SD)	Unadjusted mean change in EQ5D with first anti-TNF (SD)	EQ5D 12 months after first failure, mean (SD)	Mean follow-up 12 months after first failure, years (SD)	Unadjusted mean change in EQ5D over 12 months following first failure, (SD)	Adjusted* mean change in EQ5D over 12 months following first failure, (95% CI)
Stoppers (202)	1.50 (0.33)	0.33 (0.26)	0.33 (0.26)	0.50 (0.29)	0.01 (0.19)	0.32 (0.27)	1.00 (0.15)	-0.01 (0.23)	ref
Stayers (609)	1.61 (0.41)	0.35 (0.26)	0.41 (0.25)	0.61 (0.29)	0.07 (0.21)	0.44 (0.23)	1.01 (0.12)	0.03 (0.23)	0.05 (0.01, 0.09)
All Switchers (534)	1.56 (0.34)	0.32 (0.26)	0.38 (0.24)	0.56 (0.33)	0.06 (0.21)	0.42 (0.26)	1.01 (0.12)	0.05 (0.25)	0.06 (0.02, 0.11)
Early switchers (279)	1.60 (0.34)	0.33 (0.26)	0.40 (0.24)	0.60 (0.33)	0.07 (0.24)	0.46 (0.25)	1.00 (0.12)	0.06 (0.24)	0.08 (0.04, 0.13)

* Adjusted for age, gender, disease duration, HAQ score at first failure, DAS score at start of first therapy and DAS score at first failure.

6. Summary

The BSRBR continues to be a successful endeavour. Recruitment targets have been reached and good quality follow-up data continues to accrue. This success has, in part, been due to the dedication of rheumatology departments across the country to continue to monitor patients receiving anti-TNF closely and to provide the arc EU at The University of Manchester with detailed follow-up data.

Since the introduction of anti-TNF therapy for the treatment of RA, sequential use of anti-TNF therapy has slowly decreased. It is not clear whether this is due to a better response to the first anti-TNF and thus a reduced need to switch, a lower observed follow-up time in later years, or the availability of other treatment options.

We have found that patients who fail one anti-TNF for inefficacy are more likely to fail a second anti-TNF for inefficacy. A similar pattern was observed for patients stopping for an adverse event (more likely to stop a second anti-TNF for an adverse event). However, we found patients who switched following an adverse event were significantly less likely to stop their second drug for inefficacy compared to the overall risk of stopping a first anti-TNF for inefficacy, indicating that these patients are likely primary responders to anti-TNF therapies.

Following inefficacy to a first anti-TNF, the net gain in HAQ score with a second anti-TNF is small. This in part may be limited by the responsiveness of the HAQ score in patients with the most severe RA. However, this small change did map onto an important difference in EQ5D score.

This study is limited by the observational nature of the data and the non-randomised assignment to treatment, which does mean that although we have attempted to adjust our analyses for measured confounders, unmeasured confounding may still be influencing our data. Although we were able to include all patients who switched anti-TNF therapy in our analysis of treatment survival, we had to exclude some patients from the analysis of HAQ score as in these patients, HAQ scores were either missing or not recorded at a time coinciding with treatment changes. However, within this

large study, we were able to still find a substantial cohort of patient data on whom to perform this analysis.

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List of Appendices

Appendix 1. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007 Jan;56(1):13-20.

Appendix 2. Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP; BSR Biologics Register. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008 Jul;47(7):1000-5.

Appendix 3. Harrison M.J., Lunt M, Verstappen SMM, Watson K, Bansback NJ, Symmons DPM. Exploring the validity of estimating EQ-5D and SF-6D utility values from the Health Assessment Questionnaire in patients with inflammatory arthritis. Health Qual.Life Outcomes. [Under review]. 2009.

Exploring the validity of estimating EQ-5D and SF-6D utility values from the Health Assessment Questionnaire in patients with inflammatory arthritis

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Abstract

Background:

Utility scores are used to estimate Quality Adjusted Life Years (QALYs), applied in determining the cost-effectiveness of health care interventions. In studies where no preference based measures are collected, indirect methods have been developed to estimate utilities from clinical instruments.

Objective

To evaluate a published method of estimating the EQ-5D and SF-6D (preference based) utility scores from the Health Assessment Questionnaire (HAQ) in patients with inflammatory arthritis.

Methods

Data were used from 3 cohorts of patients with: early inflammatory arthritis (<10 weeks duration); established (>5 years duration) stable rheumatoid arthritis (RA); and RA being treated with anti-TNF therapy. Patients completed the EQ-5D, SF-6D and HAQ at baseline and a follow-up assessment. EQ-5D and SF-6D scores were predicted from the HAQ using a published method. Differences between predicted and observed EQ-5D and SF-6D scores were assessed using the paired t-test and linear regression.

Results

Predicted utility scores were generally higher than observed scores (range of differences: EQ-5D 0.01 - 0.06; SF-6D 0.05 - 0.10). Change between predicted values of the EQ-5D and SF-6D corresponded well with observed change in patients with

established RA. Change in mapped SF-6D scores was, however, less than half of that in observed values ($p<0.001$) in patients with more active disease. Predicted EQ-5D scores underestimated change in cohorts of patients with more active disease.

Conclusion

Predicted utility scores overestimated baseline values but underestimated change. Predicting utility values from the HAQ will therefore likely underestimate QALYs of interventions, particularly for patients with active disease. We recommended the inclusion of at least one preference based measure in future clinical studies.

The assessment of the cost-effectiveness of health care interventions has become increasingly important as health care providers aim to select the treatments and interventions which maximise health gain from their scarce resources. Assessments based on quality-adjusted life years (QALYs) are used to compare the benefits of interventions across medical conditions. The calculation of QALYs involves weighting duration of life by a preference-based measure of the health-related quality of life (HRQol) experienced. Preference based measures provide a value (known as utility), on a scale ranging from 1 (equivalent to full health) to 0 (equivalent to death) with the potential in some measures for states considered 'worse than death.' The calculation of cost per QALY as a basis for assessing the cost-effectiveness of a treatment has been adopted by organisations evaluating and recommending treatments in many countries including the UK,(1) and the USA.(2)

Preference based measures such as the EuroQol EQ-5D (3) and the SF-6D(4) (which is derived from the SF-36(5)) collect information about the health status of patients using self-administered questionnaires. The health status of the patient is then linked to a societal utility value obtained via large valuation studies in the general population which attribute a utility value to each possible health state described by the questionnaire.

In rheumatology, most clinical studies incorporate the Health Assessment Questionnaire (HAQ), which is a condition-specific health status measure that focuses on functional disability, a single aspect of health. Condition-specific health status measures have limited use in economic evaluation because comparison across therapeutic areas becomes almost impossible. Since treatments for rheumatology

have to ‘compete’ with treatments for other diseases, the comparison of cost-effectiveness using generic outcome measures is essential.

Despite their importance, many studies do not collect generic preference based utility measures. To overcome this limitation, methods of estimating the utility values of preference based measures from disease specific measures have been developed. In rheumatology, a model has recently been developed which maps the HAQ to the EQ-5D and SF-6D(6). The use of mapping techniques has been described as second-best compared to primary collection of data (7), but remain one of the most practical solutions available when no utility measure has been collected. Since preference based measures add to patient burden, and are often seen as less important than clinical outcome measures, it might also be deemed necessary to use these mapping functions in future studies. In these circumstances, the performance of the mapping function in estimating utility values needs to be assessed and the likely impact of decisions based on these estimates considered. Data supporting the construct validity and responsiveness of the SF-6D derived from the HAQ (6) has been reported in patients with early aggressive RA(8). However, to date there has been no evaluation of EQ-5D values mapped from the HAQ, and neither EQ-5D nor SF-6D scores mapped from the HAQ have to date been compared with actual measured values. The aim of this study was to evaluate the published method of estimating mean EQ-5D and SF-6D utility scores from the Health Assessment Questionnaire (HAQ), by comparing measured and mapped values in groups of patients with inflammatory arthritis with varying arthritis states and degrees of disease severity.

Methods

Patients and Setting

Data were taken from three cohorts of patients. The first was The Steroids in Very Early Arthritis (STIVEA) randomised controlled trial (RCT) of intramuscular steroid treatment versus placebo in patients with very early inflammatory arthritis (4–11 weeks duration). The trial follow-up finished in late 2007.(9) The second cohort comprised patients from the British Rheumatoid Outcome Study Group (BROSG) RCT of aggressive versus symptomatic control of inflammation in patients with established (>5 years duration) stable, symptomatic rheumatoid arthritis (RA) followed for three years. The BROSG trial was conducted between 1998 and 2001 (10). The third cohort was a sub-sample from the British Society for Rheumatology Biologics Register (BSRBR) of UK RA patients receiving anti-TNF therapy.

The BSRBR was established in October 2001, and the methods of this study have been described in detail previously.(11) Briefly, the first 4000 RA patients starting each anti-TNFα therapy were required by The National Institute for Health and Clinical Excellence (NICE) to be registered with the BSRBR and followed up for information on drug use, disease activity and adverse events. Routine data collection includes the HAQ and SF-36. As part of the current study, from 1st August 2006 to 31st December 2007, patients were also asked to complete the EQ-5D at baseline and the 6 month assessment.

The data from these three cohorts reflect a wide range of arthritis states/severity found in routine practice. Baseline data for all cohorts, included age, sex and disease

duration. Patients also completed the EQ-5D(3), and the SF-36(5) which is used to calculate the SF-6D utility measure(4). The HAQ (adjusted for aids/devices and help from others), a measure of functional disability, a patient global assessment, the 28 tender and swollen joint counts and the erythrocyte sedimentation rate (ESR) were collected, and the Disease Activity Score (DAS-28) was calculated.

Statistical Methods

Baseline characteristics were summarised and compared between cohorts using the Kruskal-Wallis test for continuous variables and the Chi-square test for categorical variables.

Estimated EQ-5D and SF-6D scores were calculated from the HAQ, using the most successful of the methods described in the article by Bansback et al (6). EQ-5D and SF-6D scores were estimated using linear regression models estimated by generalising estimating equation algorithms with a first order autoregressive correlation matrix structure. The EQ-5D was estimated using model 5, which was based on all 42 items of the HAQ (20 used to make the domain scores, and 22 aids/devices/help items), and treating each as a categorical variable(6). The SF-6D was estimated using model 2 from the paper which used the 8 HAQ domain scores, treated as a continuous variable. These models were reported to have the lowest mean square error and the best predictive value of the five methods.

The associations between the HAQ, EQ-5D and SF-6D were tested using Spearman's rank. Mapped and observed EQ-5D and SF-6D scores were compared at baseline and

in terms of the change between baseline and the final follow-up. The mean difference between mapped and observed values were calculated and presented with 95% confidence intervals and a 95% reference range. The correlations of observed and predicted values for each measure were assessed using the R^2 statistic from a linear regression and differences between observed and predicted scores tested using the paired t-test.

Results

Cross-sectional analysis

265 patients recruited to STIVEA, 466 to BROSG, and 866 patients from the BSRBR received a baseline EQ-5D and SF-36 questionnaire. 1472 patients completed and returned all the baseline questionnaires and were included in this analysis; 224 (85%) of the STIVEA cohort, 453 (97%) of the BROSG cohort, and 795 (92%) of the BSRBR patients.

There were significant differences in demographic and clinical characteristics between the three groups (Table 1). Patients from the BROSG study were older (median (IQR): 62 (51, 67)) than those from STIVEA (median (IQR): 59 (44, 66)) and BSRBR (median (IQR): 59 (51, 67)) studies, and had lower DAS28 scores (median (IQR): BROSG 4.0 (3.2, 4.9) vs. STIVEA 5.5 (4.8, 6.4) and BSRBR 6.0 (5.1, 6.8)) and lower median tender (median (IQR): BROSG 3 (1, 8) vs. STIVEA 9 (5, 15) and BSRBR 12 (6, 19)) and swollen joint counts (median (IQR): BROSG 3 (1, 6) vs. STIVEA 8 (5, 12) and BSRBR 7 (4, 12)). There was a trend of increasing HAQ score with

increasing disease duration (i.e. STIVEA>BROSG>BSRBR), but only the difference between patients in the STIVEA (median (IQR) 1.3 (0.6, 1.6)) and BSRBR (median (IQR) 1.8 (1.1, 2.1)) studies was statistically significant ($p<0.001$). There were proportionally more women in the BSRBR study (76%) than the BROSG (68%) or STIVEA (72%) studies ($p=0.003$). Baseline correlations of HAQ and EQ-5D scores ranged from 0.63 (BROSG & BSRBR) to 0.69 (STIVEA), and between HAQ and SF-6D from 0.58 (BROSG) to 0.68 (STIVEA & BSRBR).

Overall, the correlations between observed and predicted SF-6D (R^2 0.34 - 0.51) scores were higher than for the EQ-5D (R^2 0.20 - 0.35) (Table 2). The mapped mean (SD) baseline EQ-5D in established RA patients did not differ from observed values (EQ-5D: observed 0.59 (0.22) vs. mapped 0.59 (0.19), $p=0.494$). The predicted mean EQ-5D values were significantly higher than the observed values in patients with early arthritis, (observed 0.47 (0.31) vs. mapped 0.54 (0.25), $p<0.001$) and those eligible for anti-TNF therapy (observed 0.40 (0.33) vs. mapped 0.44 (0.26), $p<0.001$). The variance around all mapped utility values was consistently lower than that around observed values i.e. the mapped values were falsely precise.

Predicted SF-6D scores were consistently higher than observed scores (Table 2) across all cohorts. The predicted mean baseline SF-6D in established RA patients was a small over-estimate (observed 0.64 (0.13) vs. mapped 0.69 (0.05), $p<0.001$). However, mapped SF-6D values were considerably higher than observed values in patients with early arthritis (observed 0.57 (0.13) vs. mapped 0.67 (0.07), $p<0.001$) or those eligible for anti-TNF therapy (observed 0.53 (0.11) vs. mapped 0.65 (0.06), $p<0.001$).

Longitudinal analysis

Complete EQ-5D, SF-6D and HAQ details were available for 1283 patients at baseline and the final follow-up assessment. The HAQ scores of patients in the STIVEA trial (1 year mean change -0.38 (SD 0.66)) and BSRBR study (6 month mean change -0.27 (SD 0.87)) improved over the follow-up period. The mean HAQ score of patients in the BROSG trial deteriorated (3 year mean change 0.16 (SD 0.47)). There was moderate correlation of change in HAQ with change in EQ-5D in STIVEA (r=0.58) and with change in SF-6D in STIVEA (r=0.68) and BSRBR (r=0.53). Lower correlations of change in HAQ and EQ-5D were observed in BROSG (r=0.33) and BSRBR (r=0.42) and with the SF-6D in BROSG (0.31).

The correlations between change in observed and predicted SF-6D scores (R^2 0.33 - 0.46) were higher than for the EQ-5D (R^2 0.08 - 0.22) (Table 3). Change in predicted values of the EQ-5D (mean difference 0.00, 95%CI -0.02, 0.03) and SF-6D (mean difference -0.0003, 95%CI -0.01, 0.01) corresponded very well with observed change in patients from the BROSG study, a group with established disease. The change in mapped and observed EQ-5D scores was also very similar in patients receiving anti-TNF therapy (mean difference -0.01 (-0.04, 0.01).

Mapped EQ-5D scores significantly underestimated change in patients with early arthritis (mean difference -0.07, 95% CI -0.12, -0.03). The mean change in mapped SF-6D scores was less than half that in observed values in patients with early arthritis (SF-6D: observed 0.13 (SD 0.16) vs. mapped 0.04 (SD 0.07), $p<0.001$) and severe RA

(SF-6D: observed 0.05 (SD 0.12) vs. mapped 0.02 (SD 0.06), $p<0.001$). There was no significant difference in change using mapped and observed SF-6D values in the BRSOG trial.

Discussion

We found that, using the method of Bansback et al (6), the accuracy of estimating utility scores from the HAQ varies according to disease activity and duration. Mapped values overestimated values cross-sectionally and underestimated change in patients with active arthritis, particularly those with very early disease. Predicted SF-6D values overestimated baseline values and underestimated improvement in patients with active disease by approximately 60-70%. Estimating change in EQ-5D and SF-6D scores in patients with more stable established disease was more accurate. Overall, EQ-5D scores mapped from the HAQ were more accurate than SF-6D scores mapped from the HAQ.

Evaluations of QALYs derived by mapping from the HAQ may provide conservative estimates of cost-effectiveness of treatments. In other words, the number of QALYs gained by the treatment may be underestimated and so the cost per QALY will appear higher than it actually is. Conservative cost-effective ratios might therefore incorrectly impact on the decisions by organizations such as NICE in the UK(1), increasing the likelihood of truly cost effective treatments being rejected if mapped utility values were used. A recent study estimating EQ-5D values from the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index also reported that QALY gains and cost per QALY estimated using mapped and actual EQ-5D values were very

different. Our study emphasizes the need, in future studies, to incorporate preference based instruments such as the EQ-5D or SF-36 or SF-12 which allow the calculation of the SF-6D (4;12), and supports the similar recommendations made by Barton et al (13).

During the analysis for this study we attempted to develop a consistent model to estimate the EQ-5D and SF-6D from the HAQ using the three cohorts of patients reflecting a range of arthritis states and severity of disease. We performed closed-test comparisons for alternative fractional polynomial model specifications but found no improvement on the model specified by Bansback et al (6). We also attempted to use the additional covariates of age, sex, disease duration and DAS28 score, but remained unable to develop a prediction model which explained the difference in the relationship between the HAQ and EQ-5D/SF-6D within our three cohorts.

As expected (14) we found that predicted utility scores have smaller variance than observed values. This is because mapped values lack the within person variance found in observed values. Therefore, in addition to mapped utility values resulting in an inflated cost per QALY estimate, the probability of a treatment being cost-effective at a specified level of willingness to pay (e.g. £20-30k in the UK), which is driven by uncertainty around the cost and effect parameter estimates, will also be overestimated. One way to solve this particular issue is to use multiple imputation of utility values, rather than a single imputation as performed here.

The data in this study suggest that, in certain situations, mapping from the HAQ to the EQ-5D or SF-6D would be acceptable. Would it be better to estimate the EQ5D or

SF6d? Overall, using direct measurement, the EQ-5D has been shown to correlate more strongly with measures of functional disability and damage than the SF-6D in previous studies in RA (15;16), although Scott et al.(17) reported poor correlation over time between the EQ-5D and HAQ (r=0.08). We found that correlation of the observed and predicted EQ-5D scores (R^2) was lower than the correlation between observed and predicted SF-6D scores. The EQ-5D has a known non-normal, almost bi-modal, distribution (17), and it may be the inability to predict EQ-5D values in the extremes of this distribution which increases the variance and reduces the R^2.

Although the high R^2 for the correlation between observed and predicted SF-6D scores suggests the potential for mapping between the HAQ and SF-6D, the systematic differences between observed and predicted SF-6D scores are worrying since they suggest that mapping introduces bias. The poorer performance of mapped utility values in patients with more active disease, where pain and fatigue may play a greater role, counsels against mapping utility scores for measures of functional disability alone in this context.

In conclusion, we suggest that estimation of utility values from the HAQ in studies of patients with inflammatory arthritis should be undertaken with caution, particularly in those with active disease. On the basis of the difference between observed and predicted scores, mapping of the EQ-5D from the HAQ appeared to be more valid than mapping the HAQ to the SF-6D, particularly in patients with established stable disease. Further research is required to determine whether EQ-5D and SF-6D values in patients with more active disease, can be predicted using extra covariates (as well as the HAQ). However estimating utility scores is demonstrably inferior to collecting

the utility measures as part of a study. Our findings support the recommendations of OMERACT, and more recently Barton et al (13) to include at least one measure of HRQoL, specifically one which allows the estimation of utilities, in all relevant clinical studies.

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Appendix

THE MEMBERS OF THE BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER (BSRBR)

Musgrave Park Hospital, Belfast (Dr Allister Taggart); Cannock Chase Hospital, Cannock Chase (Dr Tom Price); Christchurch Hospital, Christchurch (Dr Neil Hopkinson); Derbyshire Royal Infirmary, Derby (Dr Sheila O'Reilly); Russells Hall Hospital, Dudley (Dr George Kitas); Gartnavel General Hospital, Glasgow (Dr Duncan Porter); Glasgow Royal Infirmary, Glasgow (Dr Hilary Capell); Leeds General Infirmary, Leeds (Prof Paul Emery); King's College Hospital, London (Dr Ernest Choy); Macclesfield District General Hospital, Macclesfield (Prof Deborah Symmons); Manchester Royal Infirmary, Manchester (Dr Ian Bruce); Freeman Hospital, Newcastle-upon-Tyne (Dr Ian Griffiths); Norfolk and Norwich University Hospital, Norwich (Prof David Scott); Poole General Hospital, Poole (Dr Paul Thompson); Queen Alexandra Hospital, Portsmouth (Dr Fiona McCrae); Hope Hospital, Salford (Dr Romela Benitha); Selly Oak Hospital, Selly Oak (Dr Ronald Jubb); St Helens Hospital, St Helens (Dr Rikki Abernethy); Haywood Hospital, Stoke-on-Trent (Dr Andy Hassell); Kings Mill Centre, Sutton-In Ashfield (Dr David Walsh).

Table 1: Baseline characteristics of patients from the three cohorts, ranked by median HAQ score

	STIVEA n=224	BROSG n=453	BSRBR n=795	p-value*
Age (years)	59 (44, 66)	62 (53, 69)	59 (51, 67)	<0.001
Disease duration (years)	0.16 (0.12, 0.19)	11 (7, 16)	9 (3, 18)	<0.001
Female gender, n(%)	160 (72%)	308 (68%)	604 (76%)	0.009†
HAQ	1.3(0.6, 1.6)	1.5 (0.9, 2.0)	1.8 (1.1, 2.1)	<0.001
DAS28	5.5 (4.8, 6.4)	4.0 (3.2, 4.9)	6.0 (5.1, 6.8)	<0.001
28-Tender joint count	9 (5, 15)	3 (1, 8)	12 (6, 19)	<0.001
28-Swollen joint count	8 (5, 12)	3 (1, 6)	7 (4, 12)	<0.001

Values are median (IQR) unless otherwise stated. * Kruskal-Wallis; † Chi-square

Table 2: Comparison of baseline observed and mapped utility scores

	n	Mapped Mean (SD	Estimated (Mean (SD)	R^2	Difference (Estimated-Mapped) Mean (95% CI)	95% reference range
EQ-5D						
STIVEA	224	0.47 (0.30)	0.53 (0.25)	0.35	0.06 (0.02, 0.09)	-0.44 to 0.56
BROSG	453	0.59 (0.22)	0.59 (0.19)	0.20	0.01 (-0.01, 0.03)	-0.42 to 0.44
BSRBR	795	0.40 (0.33)	0.44 (0.26)	0.35	0.04 (0.02, 0.06)	-0.49 to 0.57
SF-6D						
STIVEA	224	0.57 (0.13)	0.67 (0.07)	0.45	0.10 (0.09, 0.11)	-0.09 to 0.29
BROSG	453	0.63 (0.13)	0.68 (0.07)	0.34	0.05 (0.04, 0.05)	-0.16 to 0.25
BSRBR	795	0.53 (0.11)	0.63 (0.07)	0.51	0.09 (0.09, 0.10)	-0.06 to 0.25

Table 3: Change in observed and mapped utility scores

Study, follow-up	n	Mapped Mean (SD	Estimated (Mean (SD)	R^2	Difference (Estimated-Mapped) Mean (95% CI)	95% reference range
EQ-5D						
STIVEA, 1-year	159	0.20 (0.31)	0.12 (0.24)	0.22	-0.07 (-0.12, -0.03)	-0.50 to 0.64
BROSG, 3-year	375	-0.06 (0.24)	-0.06 (0.24)	0.08	-0.00 (-0.02, 0.02)	-0.50 to 0.50
BSRBR, 6-month	749	0.08 (0.33)	0.07 (0.25)	0.19	-0.01 (-0.04, 0.01)	-0.60 to 0.63
SF-6D						
STIVEA, 1-year	159	0.13 (0.16)	0.04 (0.07)	0.46	-0.09 (-0.11, -0.07)	-0.14 to 0.33
BROSG, 3-year	375	-0.02 (0.11)	-0.02 (0.05)	0.11	-0.00 (-0.01, 0.01)	-0.21 to 0.21
BSRBR, 6-month	749	0.05 (0.12)	0.02 (0.06)	0.33	-0.03 (-0.03, -0.02)	-0.16 to 0.21

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