Technology Assessment

Technology Assessment Program

Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, Maryland 20850

MODELING THE COST EFFECTIVENESS OF ETANERCEPT, ADALIMUMAB AND ANAKINRA COMPARED TO INFLIXIMAB IN THE TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS IN THE MEDICARE PROGRAM

12 Oct 2006

MODELING THE COST EFFECTIVENESS OF ETANERCEPT, ADALIMUMAB AND ANAKINRA COMPARED TO INFLIXIMAB IN THE TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS IN THE MEDICARE PROGRAM

FINAL REPORT

Allan Wailoo[1], Alan Brennan[1], Nick Bansback[1,2], Richard Nixon[3], Fred Wolfe[4], Kaleb Michaud[4,5].

[1] Health Economics and Decision Science, University of Sheffield, UK
[2] Centre for Health Evaluation and Outcome Sciences, University of British Columbia, Canada
[3] University of Cambridge, UK
[4] National Databank for Rheumatic Diseases, US
[5] Center for Primary Care and Outcomes Research, Stanford University, US.

This report is based on research conducted by the School of Health and Related Research, The University of Sheffield under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. RFQ 04R000206). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

EXECUTIVE SUMMARY

The Medicare Prescription Drug Improvement and Modernization Act of 2003 brings some of the most substantial changes to the Medicare program since its inception in 1965. Under one part of the Act, drug coverage will be expanded in January 2006 and one area where this is expected to have significant impact is Rheumatoid Arthritis (RA). Until this point, Medicare only covered one drug (infliximab) in a class of newer, so called "biologic" drugs used to treat RA. Beginning in January 2006, Prescription Drug Plans charged with administering the new benefit have the option of including all of these drugs in their formularies.

Part of the Act mandated the Medicare Replacement Drug Demonstration Program which ran between September 2004 and December 2005. As part of the evaluation of the demonstration program, this report assesses the cost effectiveness of some of the additional treatment strategies that will become available with this enhanced coverage.

A decision analytic model is developed to assess the cost effectiveness of etanercept, adalimumab or anakinra in comparison to infliximab alone. The model is also used to assess the cost effectiveness of using a second or third biologic drug in a sequence of treatment compared to infliximab alone.

Two key sources of information are exploited in order to populate the model. First, we conducted analyses of the National Databank for Rheumatic Diseases, a detailed disease registry comprising in excess of 17,000 patients. Second, meta-analysis of randomised controlled trials data was undertaken. The model estimates the incremental cost per quality adjusted life year (QALY) from a Medicare viewpoint using probabilistic sensitivity analysis to express uncertainty in model parameters. Several scenarios are presented to reflect additional model uncertainties.

Base case results indicate that infliximab, etanercept and adalimumab are very similar in terms of effectiveness but that infliximab is a substantially more expensive strategy. Anakinra is the least effective strategy but is also considerably less expensive. One important factor identified by sensitivity analysis is the dose of infliximab. If the dose of infliximab is assumed to remain at the recommended starting does of 3mg/kg then infliximab may be less costly and thereby cost effective. However, the key driver of differences between the strategies is the cost of the drugs themselves.

Base case analyses of sequential biologic drug strategies generate extremely high cost effectiveness ratios compared to infliximab alone. The lowest incremental cost per QALY is $133k for a strategy of etanercept followed by adalimumab. Three important parameter values are identified in sensitivity analysis; the probability of 6 month response; the rate of disease progression after withdrawal from biologic; and the discount rates used for costs and benefits.

CONTENTS

TABLES, BOXES AND FIGURES

Tables

Figures

Boxes

ABBREVIATIONS

American College of Rheumatology (ACR)
Adalimumab (ALB)
Anakinra (AKA)
Centers for Medicare & Medicaid Services (CMS)
Cost Effectiveness Acceptability Curve (CEAC)
Disease Activity Score (DAS)
Disease Modifying Antirheumatic Drugs (DMARDs)
Etanercept (ETP)
European League Against Rheumatism (EULAR)
Expected Value of Perfect Information (EVPI)
Health Assessment Questionnaire Disability Index (HAQ-DI)
Incremental Cost Effectiveness Ratio (ICER)
Infliximab (IXB)
Interleukin-1 Receptor Antagonist (IL-1Ra)
Maximum Acceptable Incremental Cost Effectiveness Ratio (MAICER)
Methotrexate (MTX)
National Databank for Rheumatic Diseases (NDB)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Quality Adjusted Life Year (QALY)
Randomized Controlled Trial (RCT)
Rheumatoid Arthritis (RA)
Tumour Necrosis Factor α (TNF α)

1. INTRODUCTION

1.1. BACKGROUND

Rheumatoid arthritis and its treatment

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease that affects approximately 1% of US adults, a total of 2.1 million persons of whom 600,000 are male and 1.5 million female [Lawrence,1998]. In 2002, an estimated 832,000 Medicare beneficiaries were diagnosed with RA (CMS estimates from the Medicare Current Beneficiary Survey). RA affects the physical functioning of patients, their psychological and social health, and eventually progresses to substantial disability through the loss of mobility, increased co-morbidity and premature mortality [Yelin, 1995; Pincus, 1993; Wolfe, 2003; Wong, 2001]. The economic burden of RA to society is substantial. A mean loss of $6,287 annual household income has been estimated [Wolfe et al., 2005] and the overall impact of RA has been estimated to approximate that of treating ischaemic heart disease [Callahan, 1998].

Conventional treatment for RA involves a multidisciplinary approach that includes education, physical and occupational therapy, and combinations of two classes of drugs: non-steroidal anti-inflammatory drugs (NSAIDs); analgesics; corticosteroids; and disease modifying antirheumatic drugs (DMARDs) [American College of Rheumatology, 2002]. The first of these classes of drugs are used as 'bridge therapy' to allow for short-term control of the disease before DMARDs take effect. The latter encompasses a large class of heterogeneous drugs including sulfasalazine, antimalarials, penicillamine, gold, methotrexate (MTX), azathrioprine, leflunomide and cyclophophamide. Because of its favourable efficacy/toxicity trade-off, MTX has become the standard of care for patients with moderate to severe RA [American College of Rheumatology, 2002; Felson, 1992]. In addition, a recent analysis, Choi et al. demonstrated a significant survival benefit of those on MTX compared to other DMARDs [Choi, 2002]. However, concerns with toxicity and adverse effects, together with failure to achieve disease remission, prompt patients to discontinue or move between DMARDs [Galindo-Rodriguez, 1999].

In recent years the introduction of a newer class of "biologic" DMARDS (infliximab, etanercept, adalimumab, anakinra) has transformed the management of RA. The first three of these are tumour necrosis factor (TNF) α inhibitors. Anakinra is an interleukin-1 receptor antagonist (IL-1Ra). In RA, TNF-α and interleukin 1 (IL-1) are key pro-inflammatory cytokines, which are chemical messengers produced by activated immune cells that stimulate or inhibit various aspects of the immune response. These cytokines reproduce and encourage production of other cytokines that cause synoviocyte proliferation, cartilage destruction and bone erosions in RA. In clinical studies, inhibition of TNF-α and IL-1 have demonstrated a significant reduction in the manifestations of RA, improvement in function, and retardation of X-ray progression [Moreland, 1997; Maini, 1999; Breshinan, 1998; Weinblatt, 2003].

Biologic drugs are expensive relative to traditional DMARDs, such as MTX. A recent study in the US demonstrated that the introduction of these new treatments increases the total annual direct cost of a biologic treated patient threefold [Michaud, 2003]. In 2002, approximately 7.8% of Medicare RA beneficiaries were using these biologic

drugs [MCBS, 2002]. These additional costs make these agents natural candidates for cost effectiveness analyses (CEA). CEA compares the incremental costs of an intervention over conventional management with its incremental health benefit [Drummond, 1997]. Cost utility ratios are the most popular form of CEA since health benefit is measured in quality adjusted life years (QALYs) allowing comparisons across other diseases on the most efficient strategy for resource allocation. A number of such analyses have already been undertaken in the analysis of biologic DMARDs [Kobelt, 2003; Wong, 2002; Brennan, 2004; Jobanputra, 2002; Kobelt, 2004; Bansback, 2004]. As with current analyses undertaken on behalf of the National Institute for Health and Clinical Excellence in the UK [Chen, 2005], these studies focus on the cost effectiveness of biologics compared to traditional DMARD therapy.

The decision making context

In the US, Medicare is the nation's largest health insurance program. A government funded scheme for those over 65 years of age or with certain disabilities, Medicare provides coverage to almost 40 million Americans. However, Medicare prescription drug coverage has been limited: generally Medicare Part B coverage only extends to those drugs administered by a physician in the doctor's office or a clinic. In the case of biologic DMARDS, this means that only infliximab has been covered as this is an intravenous infusion that must be administered by a licensed medical practitioner. In 2003 the Medicare Prescription Drug Improvement and Modernisation Act (MMA) was passed. The Act establishes a voluntary prescription drug program that will extend Medicare prescription drug coverage in a number of disease areas, including RA starting in January 2006. In the meantime, the Act also called for the implementation of a Medicare Replacement Drug Demonstration (MRDD) program to provide bridge coverage for selected drugs and biologics that replace Part B medications until the introduction of the MMA. The demonstration program began in September 2004, and provided coverage to just under 50,000 beneficiaries through the end of 2005.

The purpose of the analysis presented here is to assess in terms of cost effectiveness the impact of the MRDD for beneficiaries with RA from the viewpoint of Medicare, that is, the extension of coverage from infliximab alone to include the other biologic DMARDs etanercept, adalimumab and anakinra.

1.2. RESEARCH QUESTIONS

- What is the incremental cost-effectiveness to the Medicare program of extending coverage to etanercept, adalimumab, and anakinra relative to treating beneficiaries with the currently-covered infliximab?

- What is the incremental cost effectiveness of sequential biologic drug use, either two or three biologics, compared to infliximab alone?

- How do these results differ if initial response to biologic therapy is based on data from a prospective observational cohort in the National Databank for Rheumatic Diseases rather than meta-analysis of randomized controlled trials?

- How do these results differ if the SF6D scoring algorithm is used to calculate QALYs rather than EQ5D?

1.3. FUNDING FOR THE STUDY

The study was wholly funded by a grant from the Agency for Healthcare Research and Quality (AHRQ) with funds transferred from the Centers for Medicare and Medicaid Services (CMS). [Project number RFQ 04R000206.]

1.4. CONTRIBUTORS AND CONFLICTS OF INTEREST

This project is run through the Decision Support Unit (DSU), based at the University of Sheffield. The DSU is an independent, academic unit funded by the UK NHS National Institute for Health and Clinical Excellence (NICE) to provide expert support to the institute's Technology Appraisal Program. Dr Wailoo is director of the DSU and is the main author of this report. He developed the cost effectiveness model based on previous models created by Alan Brennan and Nick Bansback. He assisted with the review of clinical trials, developed data requests to the NDB, undertook the cost effectiveness analyses and wrote the report.

Nick Bansback acted as consultant to all stages of the project. He undertook some of the initial reviews and undertook the meta-analysis of trial data. He had no involvement with the model adaptation, or how any of the analyses or assumptions were administered.

Alan Brennan acted as consultant to the project.

Richard Nixon developed the statistical requests to the NDB, undertook meta-analysis of trial data and commented on the report.

Fred Wolfe is medical and research director of the NDB. Kaleb Michaud is a Trainee in the AHRQ Fellowship Training Program at the Center for Primary Care and Outcomes Research, Stanford University. Both helped to develop the statistical approaches used to analyze the NDB, undertook those analyses, read and commented on the draft report

AW, AB, NB and RN declare no current conflict of interest. Appendix 1 outlines all related previous funding.
FW and KM declare funding in Appendix 1.

2. MATERIAL AND METHODS

2.1. OVERVIEW OF APPROACH

2.1.1. Modeling

A decision analytic model was developed, drawing on previous analyses undertaken in the UK [Brennan et al. 2005]. The model is an individual sampling model [Barton et al. 2004] used to track changes to important variables at time-points where events (starting biologic treatment, withdrawing from treatment, death) occur [Law 2000]. An essential part of the model is that it tracks hypothetical patients one at a time based on the experience of an average cohort. The time at which events occur and the results of those events is dependent on a range of characteristics specific to the individual but which are drawn from the characteristics of an average cohort.

Individual patients are followed from the time of starting treatment on a biologic until death, with changes calculated every six months. Unlike cohort model approaches, individuals take a single path through the model. At each chance event, the route taken by that individual patient is determined by a random number and the assigned probability of each event.
A sufficient number of hypothetical patients are sent through the model to give overall precision to the estimates of mean cost and utility.

2.1.2. Drugs and doses

TNF-a inhibitors

Infliximab (Remicade® - Centocor Inc.) is given by IV infusion administered by a health care professional. The recommended dose is 3mg/kg given at weeks 0, 2, 6 and then every 8 weeks thereafter. Dose may be increased up to 10mg/kg where response is “incomplete” [Centocor Inc. 2005].

Etanercept (Enbrel® - Amgen/Wyeth Pharmaceuticals) is administered by subcutaneous injection at a recommended dose of 50mg per week. Higher doses are not recommended.

Adalimumab (Humira® - Abbott) is also administered by subcutaneous injection at a recommended dose of 40mg every other week. Patients not on concomitant MTX may derive additional benefits from a dose of 40mg every week [Abbott Laboratories, 2004].

Interleukin-1 receptor antagonist

The recommended dose of anakinra (Kineret® - Amgen) is 100mg per day delivered by subcutaneous injection.

2.1.3. Data sources

Meta-analysis of Randomized Controlled Trials

The primary sources of data on the effectiveness of biologic drugs are randomised controlled trials. Full details of these trials are given in subsequent sections. It should be noted concerns have been raised about randomized controlled trial data based

estimates of response [Wolfe and Michaud, 2005]. This issue is addressed in detail in the discussion section of the document.

National Databank for Rheumatic Diseases

The National Databank for Rheumatic Diseases (NDB) is a not-for-profit rheumatic disease research databank in which patients complete detailed self-report questionnaires at 6 month intervals [Wolfe and Michaud, 2005]. Patients in the NDB are recruited from two sources: 1) non-selected patients from the practices of US rheumatologists and 2) patients enrolled as part of pharmaceutical company sponsored registries. Eligible patients in this study were those with RA who had completed a biannual survey for events occurring between July 1 1998 and June 30 2004. The resultant data set contained 17,108 RA patients and 90,769 6-month observations. Patients were referred by 1,070 U.S. rheumatologists dispersed throughout the US. More than 90% of rheumatologists were in private practice and not full time university physicians. The diagnosis of RA was made by the patients' rheumatologists. Medicare insurance coverage is reported in approximately 45% of these observations.

At each assessment, demographic variables were recorded including sex, age, ethnic origin, education level, current marital status, medical history and total family income. Patients also complete the Health Assessment Questionnaire Disability Index (HAQ-DI), EuroQol, SF-6D and a VAS QOL scale. Patients describe all medications used and provide information regarding medical treatments, physician visits and hospitalizations.

The precise number of observations used for each analysis varies and are reported in subsequent sections. The total number of patients (observations) that had never and were not currently receiving biologic drug treatment at the time of registration with the NDB and subsequently started were 1490 (12290), 1403 (11738), 74 (652) and 160 (1357) for etanercept, infliximab, anakinra and adalimumab respectively.

The NDB attracts participants that are not necessarily representative of the RA community. NDB participants tend to be from higher income backgrounds, are less likely to come from an ethnic minority and are better educated than the general RA population. Nevertheless, the NDB is one of the richest sources of data for the study of RA patients in the US. The aim of all analyses requested of the NDB was to maximise the usefulness of NDB data while maintaining relevance to the Medicare RA population. In order to achieve this, regression analyses were specified that included a number of covariates that control for the fact that patients may be different in terms of disease severity, socio economic characteristics and the fact that insurance status itself can influence treatment. These covariates are listed in Table 1.

Table 1: Covariate adjustments used in analysis of NDB

	Covariate
x_1	Age (yrs) at baseline
x_2	Disease duration (yrs) at baseline
x_3	Index of co-morbidities at baseline
x_4	HAQ-DI at baseline
x_5	Sex (0=female, 1=male)
x_6	On DMARD as well as biologic
x_7	Number of previous DMARDs
x_8	Which Biologic drug (ETP, IXB, ALB, AKA)
x_9	Insurance status (Not Medicare, Medicare over 65, Medicare under 65)
x_{10}	Total annual household income (US $'s)
x_{11}	Years of education
x_{12}	Ethnicity (non white, white)

The approach we have taken to estimating each of the functions used in the cost effectiveness modelling is that the same set of covariates be used in each case. These functions are used to adjust according to the characteristics of sampled patients in order to arrive at an unbiased estimate of mean cost and effect. The degree of multicollinearity between covariates is therefore not of concern, although caution is advised in the interpretation of some individual coefficients. For example, "Medicare insurance status" and "age" are likely to be highly correlated resulting in difficulties in separating out the effects of these covariates although other covariates are not affected [Murray, 2006, Greene, 2000]. However, since the purpose of the inclusion of these parameters is to adjust for the characteristics of sampled patients (all of whom are Medicare patients), no bias will be introduced to overall cost-effectiveness estimates. In addition, formal statistical significance is not of inherent interest here since the modelling approach adopted propagates all uncertainty in parameters and reflects that in uncertainty in the parameters of interest, namely costs and effects. Parsimonious specifications may be preferable in order to increase the efficiency of subsequent simulation in the cost effectiveness model.

Other data sources

Where necessary we have supplemented these two primary sources of data with published data sources.

2.1.4. Patient characteristics and covariate analysis

At the start of the model the baseline characteristics, age, sex, weight, disease duration, number of previous DMARDs used and HAQ-DI, are sampled from the average characteristics of the NDB Medicare patient group that have a clinical diagnosis of RA and have received a biologic drug prior to September 2004 (n= 1307). Current insurance status is asked for in the NDB survey and we define Medicare patients as all those that selected either "Medicare", "Medicare disability" or "Medicare and HMO". It should be noted that the analyses are undertaken for the Medicare population as a whole and are not undertaken for patient subgroups.

The sampling of these patients incorporates the correlation between characteristics using multivariate normal distributions in order to accurately represent the Medicare population without overstating model uncertainty. For example, where a patient is

selected whose age is greater than average then it is more likely that disease duration for that patient would also be higher.

The characteristics of the NDB Medicare population are contrasted with the Medicare RA population using data from the Medicare Current Beneficiary Survey (MCBS) in Table 2. The MCBS is a continuous, rolling, longitudinal sample of about 12,000 Medicare beneficiaries[1].

Table 2: Baseline patient characteristics from NDB Medicare population

	Mean	SD	Min	Max	MCBS
Age in years	70.13	8.3	31.81	90.14	72.53
Probability male (%)	21.29				25.9
Education (yrs)	13.09	2.26	0	17	11.77
Probability white (%)	95.18				86.5
Household annual income ($'s)	35696	24934	5000	100000	28588*
Disease duration	18.65	12.25	0.73	71.59	
Index of comorbidities (0-11)	2.88	1.9	0	11	
HAQ–DI at baseline	1.39	0.70	0	3	
Number of previous DMARDs	3.28	1.72	0	11	
Weight (lbs)	158.46	36.06			

* Note this is beneficiary income in the MCBS, not household income.

2.1.5. Probabilistic Sensitivity Analysis Approach

The uncertainty in model parameters is characterised using probability distributions. Where possible we characterised joint probability distributions for all the uncertain parameters. This was accomplished by using multivariate normal distributions to describe the correlation in uncertainty between the results of the statistical analyses. To do this, the variance covariance matrix is used to capture the joint distributions (reported in Appendix 2). Where joint distributions are not described we assume independence between the uncertainty in parameters.

Monte Carlo sampling is used to propagate the parameter uncertainty in the cost effectiveness model. This entails making random draws of the uncertain parameters from their (joint) probability distribution, running the model for each simulated set of parameters and collecting the outputs from each run.[Briggs, 2001] These are then a random sample from the induced probability distribution of model outputs. This process is known as 'probabilistic sensitivity analysis' (PSA)[O'Hagan et al. 2005]. Outputs from the model include mean costs and mean effectiveness. In comparing the cost-effectiveness of two strategies, uncertainty about incremental mean costs and effectiveness can be displayed in the incremental cost-effectiveness plane as a scatter plot of the Monte Carlo output samples. When choosing between two strategies, decision uncertainty is usually expressed graphically through the cost-effectiveness acceptability curve (CEAC), which plots the probability that one treatment is more cost-effective than the other as a function of the societal willingness to pay threshold value of a QALY [Fenwick, 2001]. Each run of the simulation generates correlated sets of output estimates for all the strategies being compared and the CEAC is a convenient way of conveying the uncertainty in these outputs taking into account this correlation.

[1] For full details see http://www.cms.hhs.gov/mcbs/Overview.asp [accessed 9th December 2005]

2.1.6. Expected Value of Perfect Information (EVPI)

Value of Information analysis (VOI) has been seen as a logical next step after PSA [Felli and Hazen, 1998] but remains little used in health technology assessment. This set of methods provide a formal framework in which the value of collecting proposed new information, and thereby reducing or eliminating uncertainty in model parameters, is calculated with respect to the impact that such reductions in uncertainty have on decision uncertainty. Additional information has a value to the extent that it reduces the probability that decision makers make a recommendation that is "incorrect" i.e. adopt a technology that is not in fact cost-effective.

In this report we report the global EVPI, that is, the expected value of eliminating all uncertainty in the model parameters. EVPI is a Bayesian approach that works by taking current knowledge (a prior probability distribution), adding in proposed information to be collected (data) and producing a posterior (synthesised probability distribution) based on all available information. This estimate, when combined with information on the numbers of patients likely to be affected by a decision and the relevant time scale in which the decision is relevant, provides a ceiling value that can be used by policy makers in informing decisions about future research in the light of proposed costs of conducting that research.

2.2. MODEL PATHWAYS DESCRIPTION

2.2.1. Single Biologic Strategies

The model pathway for the comparison of single biologic use versus infliximab alone is described in Figure 1. This pathway is described by tracking each patient's HAQ-DI over time. In a majority of RA clinical trials HAQ-DI is the primary and often sole measure of quality of life. While the HAQ was primarily designed to measure only aspects of physical function and pain, it has been shown to be highly correlated with many generic and disease-specific measures of health related quality of life.[Scott and Garrood, 2000]

Patients are sampled individually and described in terms of the characteristics outlined in section 2.1.4. The model runs each hypothetical patient through four different treatment arms i.e. infliximab as first biologic (simulating Medicare reimbursement prior to Sept 2004), etanercept, adalimumab and anakinra as first biologics. A number of regression analyses are used to estimate the parameters that the model uses in simulating the path each individual patient will take. These regressions are described in subsequent sections. From the description of the model it is clear that relevant costs and benefits of alternative strategies are generated over a timescale greater than is typically considered in clinical trials (the lifetime of the patient) and that the model therefore draws on data from different sources.

For each of the four strategies, the model estimates the probability of the individual patient achieving a less than 20% improvement in HAQ-DI, a 20-50% improvement in HAQ-DI, or a greater than 50% improvement in HAQ-DI (see section 2.3). These probabilities are estimated in two different ways: first using meta-analysis of randomised controlled trial data and second using data drawn from the NDB. A

random number is then drawn and this is used to determine the actual category of HAQ-DI response the individual achieves for each strategy.
Second, the actual HAQ-DI score for that patient is estimated as a function of the type of responder that individual is, their baseline HAQ-DI and other covariates (see section 2.4). This is based only on NDB data.

Thirdly, HAQ-DI is estimated at six monthly intervals for the duration of biologic drug treatment. Initial HAQ-DI change and long term HAQ-DI progression are estimated as separate functions since it has been shown in previous analyses that there may be a rapid improvement in disability at the start of treatment, followed by maintenance in that level of disability. In addition, this longer term progression may differ according to the degree of initial response [Bansback, 2005]. The long-term HAQ-DI progression rate function while on biologic treatment is described in Section 2.5 and this function is used to predict a patient's HAQ-DI for the duration of treatment. Duration of treatment is estimated by survival analysis described in section 2.6. All three of these functions are estimated from NDB data.

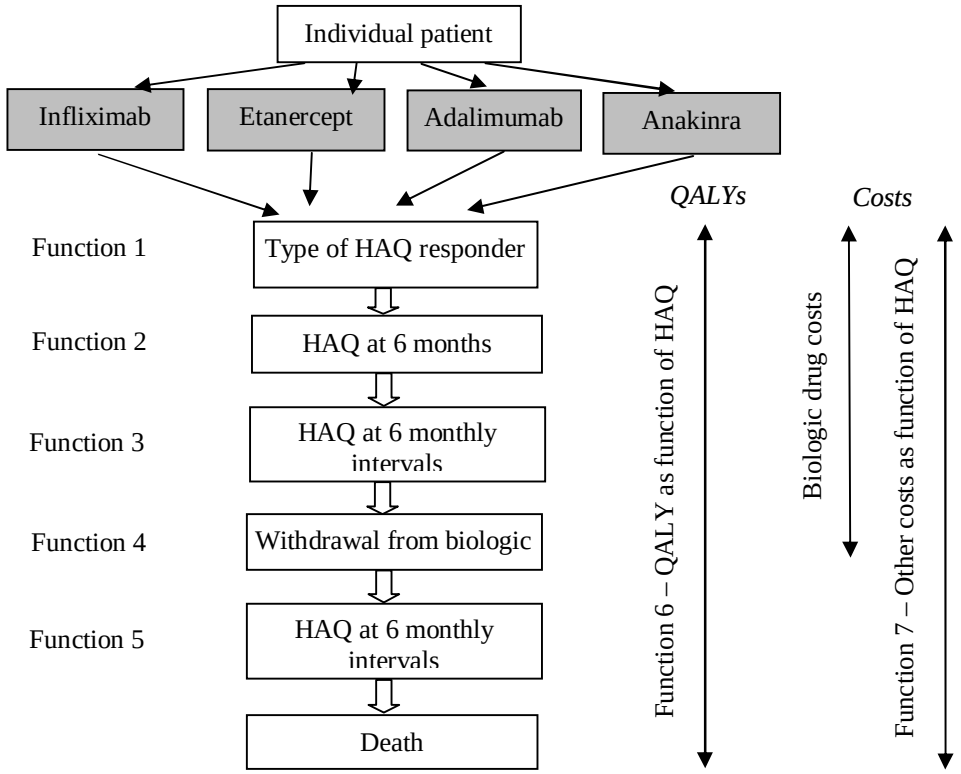
When the patient withdraws from biologic treatment, the model continues to estimate HAQ-DI progression in two stages. First, it is assumed that withdrawal often occurs due to deterioration in health, that is, the patient ceases to respond to the biologic. In order to include this in the model, we assume that at withdrawal HAQ-DI deteriorates by the same magnitude as the initial six month improvement. Second, a separate HAQ-DI progression rate while not on biologics estimated from the NDB (section 2.8) is used to estimate HAQ-DI at six monthly intervals for the remainder of the patient's lifetime.

RA adjusted life tables (section 2.12) are used to estimate time of death for each patient.

The calculated six monthly HAQ-DI profile is then converted into QALYs using the function estimated from NDB data and described in section 2.9.

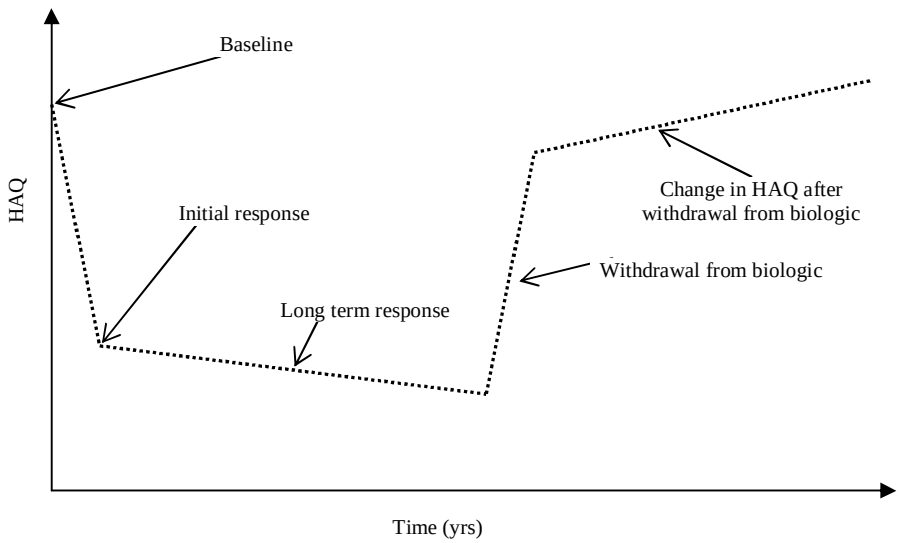
Costs are allocated in two stages. First, all Medicare borne costs are estimated as a function of HAQ-DI (and other covariates) as described in section 2.10 based on data from the NDB. Only biologic drug costs are excluded from this function since these are entered separately. In the case of infliximab the cost of administering the drug is also entered directly in the model. Model options allow for dose escalation over time and rounding up to the nearest full vial in the case of infliximab. Biologic drug costs are described in section 2.11.

Figure 1: Model schematic – single biologic use.



A typical expected HAQ-DI profile for a patient is shown in Figure 2.

Figure 2: **Expected patient progression – single biologic**.



2.2.2. Sequential biologic strategies

The model described above was amended to allow comparisons between single and multiple biologic treatment strategies. The general structure of the model is equivalent but includes a greater number of treatment strategies. Instead of simulating patients through each of four single biologic strategies (i.e. treatment with biologic until

withdrawal after which treatment with non biologic DMARDs is assumed) patients are simulated through eleven strategies which were selected to mirror a range of one and two switch options. This does not exhaust all possible options and the exclusion of a strategy does not imply anything about its cost effectiveness. These are:

1. Infliximab
2. Etanercept
3. Adalimumab
4. Infliximab → etanercept
5. Infliximab → adalimumab
6. Etanercept → adalimumab
7. Adalimumab → infliximab
8. Infliximab → etanercept→ adalimumab
9. Infliximab → adalimumab → etanercept
10. Etanercept → adalimumab→ infliximab
11. Etanercept → infliximab → adalimumab

Evidence of biologic effectiveness in those that have previously failed a biologic DMARD was reviewed (see Appendix 3). The review suggests that while TNF–α inhibitor therapy may be as effective in a sequential strategy as at first use, anakinra is less effective in those that have already failed a previous biologic. On the basis of that review, anakinra was excluded from sequential analyses.

The model proceeds as in Figure 1 above. At withdrawal from first biologic, patients move onto the next biologic in the sequence. Function 4 is therefore followed by functions 1, 2, and 3 for the next biologic in the sequence until withdrawal from the final biologic in the sequence. At that point, HAQ-DI progression is estimated using function 5.

Box 1: Main model assumptions

- For the period where withdrawal from biologic therapy occurs, patients that experienced an initial improvement in HAQ experience an increase in HAQ (worsening) equivalent to the initial decrease (improvement). There is no change in HAQ for non responders at the time of withdrawal.
- We assume that biologic drugs will have no impact on mortality since there is insufficient evidence to the contrary. Whilst this may underestimate the true impact of biologic treatments, there is no evidence that there is a differential effect between treatments so incrementally this will not effect the results of the analysis.
- A biologic treatment is tested for at least six months before a decision to withdraw is made.
- The position of a biologic in a sequential strategy of treatments does not affect the probability of response i.e. a patient that has already failed one biologic is as likely to respond to the second biologic as a patient that has not failed a biologic, allowing for the fact that several covariates will have changed (age of the patient, number of DMARDs failed, HAQ at the start of the treatment).
- In line with common guidance, future costs and benefits are discounted at 3% per annum

2.3. PROBABILITY OF RESPONSE TO BIOLOGIC AND TRADITIONAL DMARD THERAPY

In the first base case analysis, the probability of response is derived from meta regression of phase three randomised controlled trials. In the second base case analysis, this probability is derived directly from the NDB. RCT evidence is commonly considered the gold standard evidence for populating analyses of health technology assessment. However, in RA, there are concerns on the reliability and validity of RCTs in evaluating the effectiveness of treatment.[Wolfe 2004] We therefore also use observational data to estimate the effectiveness of therapies. While the results of observational data are open to more bias potentially, it is expected that by using both sources of evidence, it can be demonstrated the extent to which results are robust.

Response at six months is classified as mild (HAQ-DI improvement of less than 20%), moderate (HAQ-DI improvement 20% or greater but less than 50%), or good (HAQ-DI improvement of 50% or greater). Throughout this section, we assume that American College of Rheumatology (ACR) defined responses correspond to HAQ-DI responses. That is, an ACR20 response is considered equivalent to a 20% or greater improvement in HAQ-DI. The ACR criteria for 20% clinical improvement (the ACR20) require a 20% improvement in the tender and swollen joint count, as well as a 20% improvement in 3 of the following 5 parameters: patient's global assessment, physician's global assessment, patient's assessment of pain, degree of disability, and level of acute-phase reactant. ACR50 is equivalent but requires a 50% improvement. HAQ-DI is typically used to measure the degree of disability and as one of the components of ACR there is likely to be a close relationship between the two measures. Bansback et al. [Bansback, 2004] found supporting evidence for this assumption using data from trials of adalimumab.

META REGRESSION OF RCT DATA

A full description of this approach is given in Appendix 4 in order to illustrate methodology. The Appendix reports only ACR50 results. In summary, the meta regression is used to estimate the probability that a patient achieves ACR20 or ACR50 depending on which of the four biologic drugs the patient receives. Evidence from both placebo controlled and MTX controlled trials was identified by systematic review and incorporated into the analysis. The approach allows the synthesis of evidence to make indirect comparisons where control arms are not equivalent and/or multiple treatment arms are included that use different doses or timing regimes. Therefore, RCT evidence that would be excluded from standard meta-analysis can be included.

In total, 3 trials of anakinra were included (n=1392), 4 trials of etanercept (n=1637), 2 trials of infliximab (n=1432) and 4 trials of adalimumab (n=2233). Probabilities of response by treatment are estimated by first calculating the probability of response on MTX alone and then applying the odds ratio for treatment response. Disease duration and baseline HAQ-DI are included as covariates.

MTX model

To estimate the probability of a patient in the placebo arm achieving ACR20 or 50 after six months we consider data from the placebo arms where MTX is used.

Table 3: Logit probability of ACR20/ACR50 response - MTX

	Median	SD	95% CI	
ACR20				
Methotrexate	-0.525	0.225	-0.974	-0.079
Disease duration - mean disease duration in studies	-0.164	0.048	-0.266	-0.071
Baseline HAQ-DI - mean baseline HAQ-DI in studies	2.708	1.644	-0.513	6.076
ACR50				
Methotrexate	-1.737	0.224	-2.224	-1.333
Disease duration - mean disease duration in studies	-0.203	0.046	-0.306	-0.121
Baseline HAQ-DI - mean baseline HAQ-DI in studies	3.082	1.566	-0.132	6.373

Treatment model

In order to estimate the probability of each category of response for a patient on a single biologic (taken in conjunction with MTX), using RCT data, we use the following:

$$p_i = p_{mtx} \times OR_i / (1 - p_{mtx} \times (1 - OR_i))$$

where p = probability,
or = odds ratio
i = anakinra, etanercept, infliximab, adalimumab
mtx = methotrexate

Table 4: Log odds ACR20/ACR50 response

	Median	SD	95% CI	
OR ACR20				
Anakinra	0.581	0.19	0.214	0.964
Etanercept	1.259	0.198	0.870	1.651
Infliximab	1.239	0.202	0.851	1.648
Adalimumab	1.121	0.15	0.825	1.414
Disease duration - mean disease duration in studies	0.111	0.022	0.068	0.157
Baseline HAQ-DI - mean baseline HAQ-DI in studies	-0.965	0.64	-2.202	0.308
OR ACR50				
Anakinra	0.802	0.253	0.336	1.329
Etanercept	1.468	0.238	1.025	1.964
Infliximab	1.397	0.232	0.957	1.866
Adalimumab	1.385	0.173	1.058	1.739
Disease duration - mean disease duration in studies	0.115	0.026	0.065	0.169
Baseline HAQ-DI - mean baseline HAQ-DI in studies	-1.671	0.781	-3.203	-0.088

Table 4 shows the log odds ratio of ACR20 and ACR50 response by treatment (only one drug is used at a time in the cost effectiveness modeling), baseline disease duration and baseline HAQ-DI (both included in the cost effectiveness modeling). This is referred to as Model 2b in Appendix 4. This model comprises less assumptions than model 3 although the results are very similar. For both ACR 20 and ACR50, the

three TNF α inhibitors have comparable effectiveness and are better than anakinra. In turn anakinra is better than either placebo or MTX alone. The disease duration parameter is positive for both response types and the CIs do not span zero, indicating that a patient is expected to respond better to biologic drugs the longer they have been diagnosed with RA. The baseline HAQ-DI parameter is negative. A patient is expected to be a worse responder the higher their baseline HAQ-DI, that is the better is their baseline health.

NDB

In order to estimate the probability of HAQ-DI response (non/ moderate/ good) at six months, the sample population was restricted to patients on first biologic that have HAQ-DI recorded at 6 months after the initiation of treatment. While this substantially reduces the sample size, this restriction was considered necessary due to the fact that NDB respondents provide responses at 6 monthly intervals that do not necessarily correspond with the start of treatment (and therefore 6 month follow up). Very few patients are included that take either adalimumab or anakinra and therefore results should be treated with extreme caution.

A proportional odds cumulative Logit model (Box 2) was used.

Box 2: Statistical modeling of proportional odds cumulative Logit model for predicting type of HAQ-DI response

Let p_1 p_2 and p_3 be the probability of a HAQ response 0 (less then 20%), 1 (between 20 and 50%) or 2 (greater than 50%)

$$L_1 = \log\left(\frac{p_1}{1-p_1}\right)$$

$$L_2 = \log\left(\frac{p_1+p_2}{1-(p_1+p_2)}\right)$$

We fit the model

$$L_j = a_j - g^T x$$

To predict the probability of a HAQ response we use the equations

$$P(\text{HAQ}=1) = 1 - \frac{1}{1+e\left(g^T x - a_1\right)}$$

$$P(\text{HAQ}=2) = 1 - \frac{1}{1+e\left(g^T x - a_2\right)}$$

where γ are the coefficients for the covariates and α_1, α_2 are the cut points. The probability of a HAQ1 response is the probability of achieving at least a HAQ20% improvement i.e. this includes those that achieve a 50% or better response.

Table 5: Results of proportional odds cumulative Logit model for predicting type of response

Ordered logistic regression — Number of obs = 357; LR chi2(15) = 38.15; Prob > chi2 = 0.0009; Log likelihood -247.651; Pseudo R2 = 0.0715

	haqrcat	***Coef.***	***Std. Err.***	***z***	***P>|z|***	***[95% Conf.Interval]***	
x_1	age	-0.011	0.016	-0.670	0.501	-0.043	0.021
x_2	Disease duration (yrs)	-0.018	0.013	-1.330	0.183	-0.044	0.008
x_3	Index of co-morbidities	-0.184	0.078	-2.350	0.019	-0.337	-0.031
x_4	HAQ-DI at baseline	-0.430	0.230	-1.870	0.061	-0.880	0.020
x_5	Male	0.225	0.328	0.690	0.493	-0.418	0.868
x_6	On DMARD as well as biologic	0.224	0.375	0.600	0.551	-0.511	0.958
x_7	Number of previous DMARDs	-0.047	0.078	-0.600	0.549	-0.199	0.106
x_8	Etanercept	Reference					
x_8	Infliximab	-0.331	0.275	-1.200	0.229	-0.870	0.208
x_8	Anakinra	-0.313	0.698	-0.450	0.654	-1.681	1.056
x_8	Adalimumab	-0.025	0.633	-0.040	0.969	-1.265	1.216
x_9	Not on Medicare	Reference					
x_9	Medicare 1(over 65)	0.177	0.619	0.290	0.775	-1.037	1.390
x_9	Medicare 2 (disability)	0.322	0.425	0.760	0.448	-0.511	1.155
x_{10}	Total income	0.000	0.000	2.250	0.025	0.000	0.000
x_{11}	Years of education	-0.054	0.061	-0.890	0.373	-0.174	0.065
x_{12}	Ethnicity - white	-0.889	0.450	-1.980	0.048	-1.771	-0.007
a_1	<HAQ20% | 20-50% or >50% intercept	-1.823	1.353			-4.474	0.829
a_2	<HAQ20% or 20-50% | >50% intercept	-0.451	1.349			-3.094	2.192

A positive coefficient indicates a greater probability of response. Patients that are older, have a greater disease duration, more comorbidities, higher (worse) HAQ-DI score, are female, are not on concurrent DMARDs, have had more previous DMARDs, are better educated, and are white are on average less likely to achieve a response at 6 months. However, only comorbidities, baseline HAQ-DI, income and ethnicity achieve statistical significance at the 10% level.

Response is most likely with etanercept followed by adalimumab, anakinra and then infliximab on average although again, these differences are not statistically significant.

COMPARING THE NDB AND META –REGRESSION OUTPUT

In order to illustrate the difference between these two data sources,

Table 6 shows the predicted probability of different HAQ-DI responses for a patient with the characteristics of the mean Medicare population using the meta regression results and then the NDB results. It can be seen that response rates are substantially lower in the NDB. There is approximately a 0.06 probability of achieving a greater than 50% improvement in HAQ or etanercept and adalimumab, compared with almost 20% of patients in the clinical trial based results. Very little difference is noted between etanercept and adalimumab in either data source.

Table 6: Probability of response by drug type

	NDB				Meta regression			
Type of HAQ-DI response	**ETP**	**IXB**	**AKA**	**ALB**	**ETP**	**IXB**	**AKA**	**ALB**
Sub 20%	0.792	0.841	0.839	0.796	0.520	0.525	0.681	0.554
20% to 50%	0.145	0.113	0.115	0.143	0.287	0.293	0.210	0.266
50% +	0.062	0.046	0.046	0.061	0.192	0.182	0.109	0.180

2.4. SIX MONTH HAQ-DI ON BIOLOGIC THERAPY

Using the NDB we estimate expected 6 months HAQ-DI on biologic treatment. This is estimated separately from longer term response since initial response is considered to be of a different magnitude, related to the controlling of disease flare ups for example. One of the covariates used in this analysis is the category of HAQ-DI response at six months (section 2.3) and for this reason the subsample of the NDB population used in this analysis is again constrained to those with data collected at the start of biologic treatment.

Box 3: Statistical modeling of Initial Improvement on Biologic Therapy

To predict HAQ-DI at six months (h_6) from baseline (h_0) using logit transformations to constrain to 0:3 range

$$h_6 = l^{-1}\left(a + bl(h_0) + g^T x\right)$$

where is HAQ DI at 6 months post biologic treatment, l is the logit function and l^{-1} its inverse, α is the constant, b is the coefficient for baseline HAQ (h_0), and g are the coefficients on covariates x_1 to x_n.

If an outcome is constrained in the range a:b then to map this to the range $d:1-d$, apply the transformation

$$t_{a,b,d}(x) = \frac{(1-2d)(x-a)}{(b-a)} + d$$

e.g. transformations for HAQ-DI. The function to transform the range 0:3 to 0.01:0.99

$$t(x) = \frac{0.98x}{3} + 0.01$$

The inverse of this function is

$$t^{-1}_{a,b,d}(y) = \frac{(y-d)(b-a)}{(1-2d)} + a$$

E.g. the function to transform the range 0.01:0.99 to 0:3

$$t^{-1}(y) = \frac{(y-0.01)3}{0.98}$$

Then the Logit type function for the outcome is

$$l_{a,b,d}(x) = \log\left(\frac{t_{a,b,d}(x)}{1-t_{a,b,d}(x)}\right)$$

and the inverse logit type function for transforming back to the outcome range is

$$l^{-1}_{a,b,d}(x) = t^{-1}_{a,b,d}\left(\frac{1}{1+e^{-x}}\right)$$

Table 7: Results of multivariate regression model to predict HAQ-DI 6 months after starting biologic treatment

Source	SS	df	MS	Number of obs	357
				F(14, 342)	175.22
Model	586.078	14	41.863	Prob > F	0
Residual	81.711	342	0.239	R-squared	0.878
Total	667.789	356	1.876	Adj R-squared	0.873
				Root MSE	0.489

	haqh6c	**Coef.**	**Std. Err.**	**t**	**P>|t|**	**[95% Conf.**	**Interval]**
x_1	age	0.001	0.004	0.170	0.865	-0.006	0.007
x_2	Disease duration (yrs)	-0.002	0.003	-0.780	0.435	-0.007	0.003
x_3	Index of co-morbidities	0.002	0.015	0.140	0.890	-0.028	0.032
x_4	HAQ-DI at baseline	0.821	0.029	28.740	0.000	0.765	0.877
x_5	Male	-0.119	0.071	-1.670	0.095	-0.260	0.021
x_6	On DMARD as well as biologic	-0.025	0.074	-0.340	0.731	-0.171	0.120
x_7	Number of previous DMARDs	-0.009	0.016	-0.560	0.575	-0.039	0.022
x_9	Not on Medicare	Reference					
x_9	Medicare 1(over 65)	-0.039	0.116	-0.340	0.735	-0.267	0.189
x_9	Medicare 2 (disability)	-0.010	0.089	-0.110	0.910	-0.185	0.165
x_{10}	Total income	0.000	0.000	-0.950	0.342	0.000	0.000
x_{11}	Years of education	0.014	0.013	1.100	0.271	-0.011	0.039
x_{12}	Ethnicity - white	-0.035	0.104	-0.340	0.737	-0.239	0.169
x_{13}	HAQ<20% responder	Reference					
x_{13}	HAQ20% responder	-0.860	0.071	-12.090	0.000	-1.000	-0.720
x_{13}	HAQ50% responder	-2.463	0.096	-25.550	0.000	-2.653	-2.274
	_cons	0.069	0.287	0.240	0.809	-0.495	0.634

A white, female patient with the same characteristics as that of the mean Medicare population is predicted to achieve an 17.6% worsening in HAQ-DI if they are below HAQ20% responders at 6 months, a 35% improvement in HAQ-DI if HAQ-DI 20-50% responders and an 81% improvement in HAQ-DI if HAQ50%+ responders.

Positive coefficients indicate a lower expected improvement in HAQ-DI. Therefore, patients that are older at baseline, have a shorter disease duration, have less comorbidities, are on concomitant DMARDs, have failed a greater number of previous DMARDs, are more educated and non white are expected to achieve lesser improvements in HAQ-DI. These variables are relatively minor however and do not achieve statistical significance at customary levels.

A higher baseline HAQ-DI is a statistically significant predictor of predicted % HAQ-DI response. However, this is not surprising given that the scale is not absolute gain but percentage gain. Sex is also a statistically significant covariate in this model, predicting that males achieve greater HAQ-DI improvements.

2.5. LONG TERM RESPONSE TO BIOLOGIC THERAPY

The following model (Box 4) is estimated from all patients in the NDB while on first biologic. It excludes the final observation prior to withdrawal from first treatment in order to avoid incorporating any possible flare up into the estimation of long term

HAQ-DI progression. This is incorporated separately in the model (see section 2.7) but is not based directly on data from the NDB.

Box 4: Statistical modeling of Post 6 month Improvement in HAQ-DI on Biologic Therapy

Similar logit type functions were used as in section 2.4
We estimate

$$l(h(t)) = l(\mathrm{h}_a) + \mathrm{t}(d + g^T x)$$

Where l = logit function, h_a is six month HAQ, t= time in months between h_a and current HAQ observation
d= time coefficient
g=coefficients for covariates

Table 8: Results of multivariate regression model to predict HAQ-DI post 6 months after starting biologic treatment

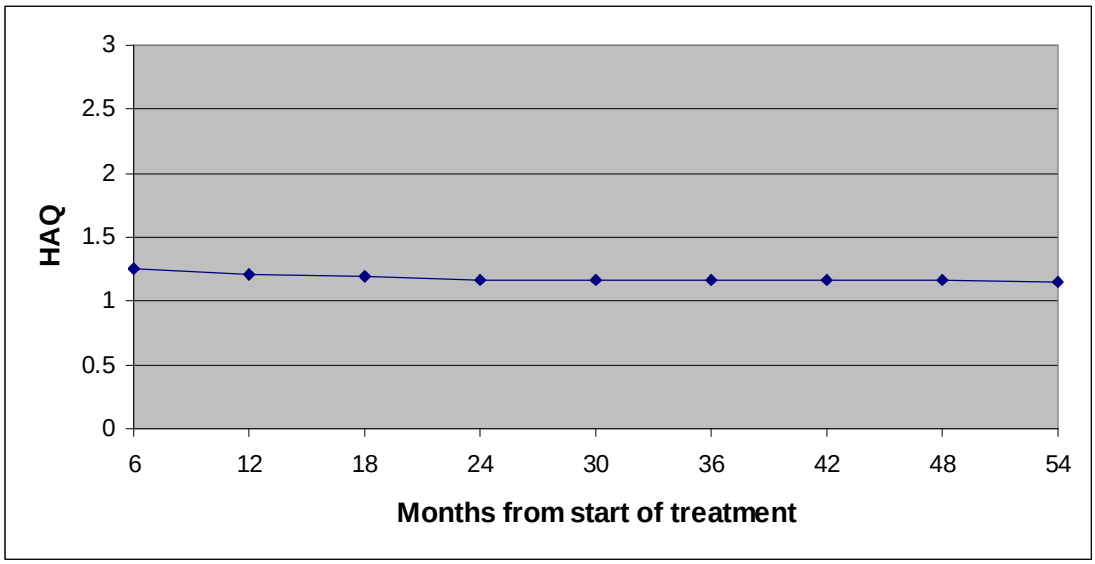
Linear regression — Number of obs 5984; F(13, 1556) 1.35; Prob > F 0.175; R-squared 0.013; Number of clusters (patkey) 1557; Root MSE 0.957

Robust

	haqh6cdif	***Coef.***	***Std. Err.***	***t***	***P>|t|***	***[95% ConfInterval]***	
t	time	-0.0125	0.0119	-1.05	0.292	-0.0357	0.0108
tx_1	age	0.0000	0.0002	0.12	0.905	-0.0003	0.0003
tx_2	Disease duration (yrs)	0.0001	0.0001	1.04	0.297	-0.0001	0.0003
tx_3	Index of co-morbidities	0.0009	0.0005	1.74	0.081	-0.0001	0.0019
tx_4	HAQ-DI at baseline	-0.0028	0.0010	-2.84	0.005	-0.0047	-0.0009
tx_5	Male	0.0010	0.0034	0.3	0.766	-0.0056	0.0076
tx_6	On DMARD as well as biologic	0.0023	0.0023	1.01	0.315	-0.0022	0.0067
tx_7	Number of previous DMARDs	0.0007	0.0007	1.01	0.313	-0.0006	0.0020
tx_9	Not on Medicare						
tx_9	Medicare 1(over 65)	0.0008	0.0020	0.41	0.684	-0.0031	0.0047
tx_9	Medicare 2 (disability)	-0.0024	0.0035	-0.68	0.499	-0.0093	0.0045
tx_{10}	Total income	0.0000	0.0000	-1.58	0.115	0.0000	0.0000
tx_{11}	Years of education	0.0006	0.0004	1.42	0.154	-0.0002	0.0015
tx_{12}	Ethnicity - white	-0.0034	0.0035	-0.97	0.334	-0.0103	0.0035

The regression results above relate to the difference between HAQ-DI at current time and HAQ-DI 6 months after the pre biologic observation, both transformed. In general the regression indicates that post 6 month HAQ-DI is virtually stable over the remaining duration of biologic treatment. For a patient with mean Medicare characteristics and a HAQ-DI of 1.25 at month 6, there is a slight improvement in health over the initial 24 months (approximately 0.04 reduction in HAQ-DI per annum) which slows over time as shown in Figure 3. This finding is consistent with published Swedish registry analysis where initial response was maintained over time [Kobelt, 2004].

Figure 3: Post 6 month HAQ-DI progression for a patient with mean Medicare characteristics



2.6. DURATION OF BIOLOGIC THERAPY – TIME TO WITHDRAWAL

The time on each biologic therapy is modelled using a Weibull survival curve based on data from the NDB.

Box 5: Weibull survival curve to estimate time on treatment

The baseline hazard function is

$$h_0(t) = \frac{a}{b^a} t^{a-1}$$

Where a is the shape, b the scale parameter and t is the time in months. A proportional hazards model is fitted, adjusting the survival for covariates.

$$h(t) = h_0(t)\exp(g^T x)$$

Where γ are the coefficients for covariates x_1 to x_{12}

The survival curve is

$$s(t) = \exp\left(-\int_0^t h(u)du\right)$$

$$= \exp\left(-\exp(g^T x)\left(\frac{t}{b}\right)^a\right)$$

Table 9: Multivariate Weibull survival analysis to predict time on 1st biologic treatment

	No. of subjects =		3112		Number of obs =		3112
	No. of failures =		1226				
	Time at risk		68229				
					LR chi2(15) =		139.68
	Log likelihood	-3297	9419		Prob> chi2 =		0
	_t	***Coef.***	***Std. Err.***	***z***	***P>|z|***	***[95% Conf.***	***Interval]***
x_1	age	0.0093	0.0040	2.31	0.021	0.0014	0.0172
x_2	Disease duration (yrs)	0.0066	0.0027	2.42	0.016	0.0012	0.0119
x_3	Index of co-morbidities	0.0979	0.0158	6.21	0	0.0670	0.1288
x_4	HAQ-DI at baseline	0.0002	0.0480	0.01	0.996	-0.0938	0.0943
x_5	Male	-0.0857	0.0783	-1.09	0.274	-0.2392	0.0678
x_6	On DMARD as well as biologic	-0.0057	0.0818	-0.07	0.945	-0.1660	0.1547
x_7	Number of previous DMARDs	0.0063	0.0180	0.35	0.725	-0.0289	0.0415
x_8	Etanercept	Reference					
x_8	Infliximab	0.0795	0.0640	1.24	0.214	-0.0460	0.2050
x_8	Anakinra	1.2122	0.1475	8.22	0	0.9232	1.5013
x_8	Adalimumab	0.0158	0.1904	0.08	0.934	-0.3575	0.3890
x_9	Not on Medicare	Reference					
x_9	Medicare 1(over 65)	0.1299	0.1251	1.04	0.299	-0.1153	0.3751
x_9	Medicare 2 (disability)	-0.0769	0.1011	-0.76	0.447	-0.2750	0.1212
x_{10}	Total income	0.0000	0.0000	-0.74	0.461	0.0000	0.0000
x_{11}	Years of education	-0.0014	0.0134	-0.11	0.916	-0.0278	0.0249
x_{12}	Ethnicity - white	-0.2382	0.1056	-2.26	0.024	-0.4451	-0.0312
K	Constant	-4.5172	0.3234	-13.97	0	-5.1511	-3.8833
$Ln\ p$	Log shape	-0.0551	0.0242	-2.27	0.023	-0.1025	-0.0076

The sign of the coefficients for each of the covariates are negatively related to time on survival. Thus patients that are older, have a longer disease duration, have more comorbidities, have a higher (worse) HAQ-DI at baseline, are female, are not taking a concomitant DMARD, are less educated or non-white spend less time on first biologic treatment.

Duration on biologic treatment is greatest for patients on etanercept (33 months for an average white, female, Medicare (over 65yrs) patient) compared to 30, 32 and 9 months on infliximab, adalimumab and anakinra respectively. The difference between anakinra and etanercept is statistically significant. Note that these figures are given by way of illustration only. The mean duration of treatment for a cohort of patients is not expected to equate the duration of treatment for a patient with average characteristics since this is not a linear function.

Medicare insurance does not have a simple relationship on duration of treatment. Medicare (over 65yrs) coverage is associated with a shorter duration on first biologic, while Medicare (under65yrs) is associated with longer duration compared to those not on Medicare.

In order to optimize the use of data from the NDB, initial response was not included as a covariate in this analysis.

2.7. WORSENING AT WITHDRAWAL FROM BIOLOGIC

Patients may withdraw from a treatment for several reasons. There may be a loss of efficacy, adverse event or a lack of insurance *inter alia*. In any event, it is assumed that patients experience a rise in HAQ in the period of withdrawal. Since NDB observations occur every six months and do not therefore necessarily coincide with treatment changes this step of the model is based on an assumption. We assume that during the period of withdrawal, patients experience a rise in HAQ-DI (worsening in health status) that is equivalent to the initial lowering in HAQ-DI experienced in the first six months of biologic treatment. This is based on results seen when patients on etanercept were discontinued and their disability quickly rebounded back to near baseline [Brennan 2004].

2.8. LONG TERM HAQ-DI AFTER WITHDRAWAL FROM BIOLOGIC THERAPY

Two alternative approaches are taken to the estimation of HAQ-DI after patients withdraw from biologic therapy. In the base case analysis we use data from the NDB. Patients that started biologic treatment while enrolled with the NDB and ended that treatment while in the NDB are included. Observations are based on the time between ending first biologic treatment and either being right censored or starting on another biologic.

A similar approach to that outlined in section 2.6 was adopted here, that is logit type transformations with time dependent covariate adjustment to estimate the difference in current HAQ-DI and first observed HAQ-DI after withdrawal from biologic.

Table 10: Results of multivariate regression model to predict HAQ-DI after withdrawal from biologic therapy

Linear regression					Number of obs		1104
					F(13, 288)		1.77
					Prob > F		0.0475
					R-squared		0.0687
Number of clusters (patkey) 289					Root MSE		0.6912
	haqh6cdif2	***Coef.***	***Std. Err.***	***t***	***P>|t|***	***[95% Conf. Interval]***	
t	time	-0.0428	0.0186	-2.3	0.022	-0.0795	-0.0062
tx_1	age	0.0004	0.0003	1.63	0.105	-0.0001	0.0010
tx_2	Disease duration (yrs)	0.0002	0.0001	1.81	0.072	0.0000	0.0005
tx_3	Index of co-morbidities	0.0008	0.0008	0.98	0.327	-0.0008	0.0023
tx_4	HAQ-DI at baseline	-0.0017	0.0012	-1.44	0.15	-0.0040	0.0006
tx_5	Male	0.0012	0.0064	0.18	0.856	-0.0114	0.0137
tx_6	On DMARD as well as biologic	0.0066	0.0028	2.4	0.017	0.0012	0.0121
tx_7	Number of previous DMARDs	0.0005	0.0009	0.62	0.539	-0.0012	0.0023
tx_9	Not on Medicare	Reference					
tx_9	Medicare 1(over 65)	-0.0025	0.0035	-0.72	0.473	-0.0095	0.0044
tx_9	Medicare 2 (disability)	-0.0063	0.0056	-1.12	0.265	-0.0173	0.0048
tx_{10}	Total income	0.0000	0.0000	1.57	0.118	0.0000	0.0000
tx_{11}	Years of education	0.0004	0.0007	0.51	0.607	-0.0010	0.0017
tx_{12}	Ethnicity - white	-0.0032	0.0046	-0.69	0.49	-0.0123	0.0059

For a patient with characteristics which correspond to the mean Medicare population, a rise in HAQ-DI of approximately 0.01 per annum is predicted. However, for patients with different characteristics, the rate varies substantially. A particularly important determinant is baseline age with younger patients experiencing much slower worsening or improvement in HAQ-DI.

In the sensitivity analysis, we estimate the annual HAQ-DI progression rate from the literature. In a paper by Scott et al, the annual progression in HAQ-DI is assessed from 12 cross sectional studies.[Scott, 2000] The weighted average of annual HAQ-DI progression, was calculated to be 0.042 (Table 11).

Table 11: Review of DMARD progression rates from Scott et al. (2000)

Study	*Year*	*N in study*	*Mean annual HAQ-DI progression*
Wolfe et al	1991	561	0.020
Lassere et al	1995	353	0.045
Sherrer et al	1986	691	0.072
Greenwood et al	1999	701	0.032
Ward et al	1993	282	0.014
Gardiner et al	1993	175	0.030
Callahan et al	1997	100	-0.006
Leymarie et al	1997	370	0.000
Ward et al	1998	182	0.017
Munro et al	1998	440	0.119
Truro cases	1998	33	0.006
Shipps Cross cases	1998	46	0.023
Crude average			0.031
Weighted average			**0.042**

To estimate the uncertainty in the average progression we use the figure of 0.58 for the individual variation for a patient with established RA over 4 to 5 years in Scott et al. To calculate the standard error, we first make this an annual variation (0.145) and then divide by the square root of n-1 (=0.0023, where n=3934).
It should be recognised that Scott et al. estimate the progression rate from studies prior to the introduction of biologic DMARDs and do not therefore directly correspond to those simulated at this stage of the model, that is, those that have failed a biologic and are on traditional DMARD therapy. Scott et al. estimate a traditional DMARD progression rate based on a mixture of patients, some of whom may never have received biologic treatment were it available and others that would. The rate should therefore be treated with caution and is used only in sensitivity analysis in this report to demonstrate the impact of using this relatively high progression rate.

2.9. TRANSLATING HAQ-DI TO UTILITY

Both SF36 and EQ5D form part of the NDB six monthly assessments. In order to estimate utility the SF6D scoring algorithm [Brazier et al. 2002] was applied. The US scoring algorithm was applied to the EQ5D [AHRQ 2005].

Multivariate regression analysis was used to estimate the relationship between utility and HAQ-DI, adjusting for covariates with clustering by patient and using logistic functions to constrain the output to a reasonable range.

This analysis uses patients enrolled in the NDB who commenced biologic therapy while enrolled but covers all time periods for those patients, both on and off biologic therapy. In addition, a fractional polynomial regression-based mapping is used to increase the sample size by 150% in the analysis of EQ5D; the components of the mapping include HAQ-II, pain VAS, mental health score (from SF36), age and sex.

Table 12: Relationship between HAQ-DI and EQ5D.

	Linear regression				Number of obs		78685
					F(6, 15406)		3009.24
					Prob > F		0
					R-squared		0.4871
	Number of clusters (patkey)		15407		Root MSE		0.7421
	eq5dus1c	***Coef.***	***Std. Err.***	***t***	***P>|t|***	***[95% Conf.***	***Interval]***
x_1	age	0.0058	0.0004	14.56	0	0.0050	0.0066
x_2	Disease duration (yrs)	0.0023	0.0004	5.29	0	0.0015	0.0032
x_4	HAQ-DI at baseline	-0.2004	0.0101	-19.76	0	-0.2202	-0.1805
x_5	Male	-0.2914	0.0118	-24.61	0	-0.3146	-0.2682
x_7	Number of previous DMARDs	0.0249	0.0028	8.9	0	0.0194	0.0304
x_{13}	Current HAQ-DI	-0.8647	0.0103	-83.57	0	-0.8850	-0.8444
K	Constant	2.0734	0.0263	78.94	0	2.0220	2.1249

Table 13: Relationship between HAQ-DI and SF6D.

	Linear regression				Number of obs		68782
					F(6, 14747)		724.01
					Prob > F		0
					R-squared		0.2769
	Number of clusters (patkey)	14748			Root MSE		0.8221
	sf6d1c	***Coef.***	***Std. Err.***	***t***	***P>|t|***	***[95% Conf.***	***Interval]***
x_1	age	0.0036	0.0005	6.95	0	0.0026	0.0046
x_2	Disease duration (yrs)	0.0027	0.0006	4.89	0	0.0016	0.0038
x_4	HAQ-DI at baseline	-0.2018	0.0098	-20.59	0	-0.2210	-0.1826
x_5	Male	-0.0245	0.0179	-1.37	0.172	-0.0597	0.0106
x_7	Number of previous DMARDs	0.0067	0.0036	1.88	0.061	-0.0003	0.0137
x_{13}	Current HAQ-DI	-0.5523	0.0106	-52.01	0	-0.5731	-0.5315
K	Constant	0.5094	0.0365	13.97	0	0.4380	0.5809

The coefficient on current HAQ-DI is smaller (-0.55) for SF6D based utilities than for the EQ5D equivalent (-0.86) indicating that as HAQ-DI improves (falls), utility will rise by a greater amount if the EQ5D is used.

2.10. TRANSLATING HAQ-DI TO COST

The NDB was used to estimate the expected resource use per patient as a function of HAQ-DI. The viewpoint of the analysis is Medicare and as such the NDB has been used to estimate only resource use that Medicare patients would be expected to consume, that is only those resources that Medicare reimburses are included in the analysis and Medicare unit prices are used to cost those resources. However, we have

not restricted the analysis to include only those patients that are Medicare registered. Non Medicare patients provide important information about the link between HAQ-DI and resource use and comprise a substantial proportion of the NDB population. We use covariates to adjust for the differences in socioeconomic characteristics between Medicare and non Medicare populations whilst maximising the explanatory power of the model and maintaining relevance to the study perspective.

Biologic drug costs are excluded from the analysis since the cost effectiveness model incorporates these costs separately.

CMS provided 2005 unit costs for medications, outpatient and hospitalisation costs. In addition to adjusting for Medicare population characteristics, covariates distinguish between time points when a patient is on a biologic drug (and which drug) versus periods when a patient is not on a biologic. This is important for the cost effectiveness model since patients are tracked over both periods. Whilst the model incorporates the costs of the biologics themselves separately, there are monitoring costs associated with biologics that are captured by this regression.

We used generalised linear models (GLMs) to estimate resource use over time. A gamma transformation was used to transform the expected skewed costs. Using this approach, the model did not converge when using data from both the Medicare and Non Medicare populations unless insurance status variables were omitted.

Table 14: GLM model of Medicare resource use by HAQ-DI

Generalized linear models		No. of obs =	63078
Optimization: ML		Residual df =	63062
		Scale parameter =	4.71
Deviance	110294. 2347	(1/df) Deviance =	1.75
Pearson	296919. 9452	(1/df) Pearson =	4.71
Variance function: V(u) = u^2		[Gamma]	
Link function: g(u) = u		[Identity]	
		AIC=	16.66
Log pseudolikelihood = -	-525529	BIC=	-586675

(Std. Err. adjusted for 11414 clusters in patkey)
Robust

	Totcmscost	***Coef.***	***Std. Err.***	***z***	***P>|z|***	***[95% Conf.***	***Interval]***
x_1	Age	7.63	0.8	9.19	0.00	6.00	9.25
x_2	Disease duration (yrs)	1.19	1.2	0.97	0.33	-1.21	3.60
x_3	Index of co-morbidities	230.74	9.7	23.73	0.00	211.68	249.80
x_4	HAQ-DI at baseline	-108.20	26.0	-4.17	0.00	-159.10	-57.30
x_{13}	Current HAQ-DI	603.79	30.2	20.01	0.00	544.66	662.92
x_5	Male	90.32	36.3	2.49	0.01	19.26	161.38
x_6	On DMARD as well as biologic	-104.06	36.0	-2.89	0.00	-174.56	-33.57
x_7	Number of previous DMARDs	81.21	9.9	8.21	0.00	61.82	100.60
x_8	Not on biologic	REF					
x_8	Etanercept	24.40	60.9	0.4	0.69	-94.88	143.69
x_8	Infliximab	87.81	47.3	1.86	0.06	-4.81	180.43
x_8	Anakinra	68.58	668.3	0.1	0.92	-1241.18	1378.34
x_8	Adalimumab	-156.99	35.4	-4.44	0.00	-226.35	-87.63
x_{10}	Total income	0.00	0.0	-0.05	0.96	0.00	0.00
x_{11}	Years of education	6.30	6.0	1.05	0.29	-5.43	18.02

x_{12}	Ethnicity – white	-43.27	47.6	-0.91	0.36	-136.49	49.95
K	Constant	-104.35	114.7	-0.91	0.36	-329.14	120.45

Results are shown in Table 14 where cost is measured in 2005 US $ per six month period. Current HAQ-DI is positively related to cost, with a 1-point deterioration (rise) in HAQ-DI associated with a $604 rise in costs although there is a negative relationship between baseline HAQ-DI and cost. Other important coefficients positively associated to cost are comorbidities, male gender, and the number of previous DMARDs. DMARD use alongside a biologic is negatively related to cost.
There is no statistically significant difference between costs whilst on any biologic versus not being on a biologic. The mean coefficient values indicate that adalimumab may be cost saving relative to no biologic treatment, although there are low numbers of patients on this drug in the NDB.

2.11. DRUG COSTS

2.11.1. Dose and unit cost assumptions

Doses for all drugs have been taken from the manufacturers recommended doses. Unit costs were supplied by CMS. For infliximab, as with other part B drugs, Medicare pays on the basis of Average Sales Price (ASP) +6%. This cost was $53.428 per 10mg as of September 2005. Part B drugs are reimbursed at 80% by Medicare so the cost per 100mg vial is $427.36. In addition, the cost per infliximab infusion was estimated from Medicare beneficiaries in the 2002 Medicare Current Beneficiary Survey with RA (n=14) at 2005 costs. The mean infusion time was 2.5hrs at a cost to Medicare of $181.

For the three drugs covered by the demonstration project, actual Medicare claims data were analysed to estimate a mean daily cost, excluding outliers (supplied by CMS). The patient cost sharing arrangements for the drugs covered by the demonstration are designed to reflect the arrangements for the part D drug benefit scheme which commences in January 2006. It was found that the mean Medicare payment under the demonstration for RA drugs is 78.5% and this was applied to all three demonstration drugs.

The daily cost for etanercept was $43.17, of which $33.88 is covered by Medicare. Adalimumab is very similarly priced at $43.37, of which $34.04 is covered by Medicare. The cost of anakinra is lower at $40.67 per day, of which Medicare covers $31.92.

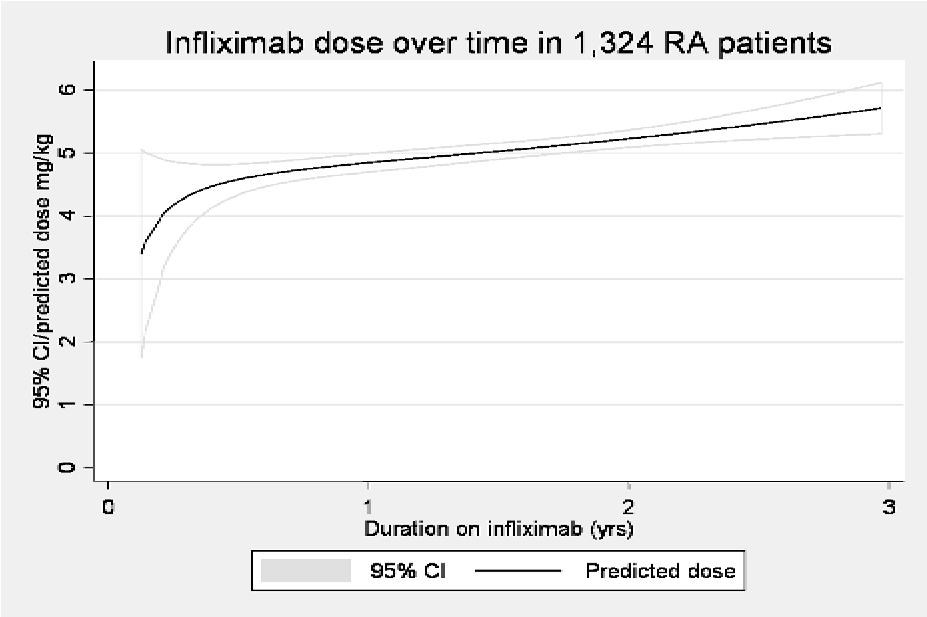
The amount of infliximab given to a patient is determined by their weight. The recommended initial dose is 3mg per kg. This is given at week 0, 2, 6 and then subsequent 8 weeks. For a 70kg patient, the cost to Medicare of infliximab itself is $898, the cost for the first six months treatment is $4936 (5.5 infusions) and for subsequent six months $2917 (3.25 infusions). However, this assumes that the 100mg vials can be divided between patients. In the base case analysis it is assumed that patients use full vials. In the case of a 70kg person, 3 vials would be used instead of 2.1.

An alternative assumption explored in sensitivity analysis is to exclude this vial rounding. This may reflect clinical practice where it may be that physicians use left over vials on the next patient in order to avoid waste.

2.11.2. Dose increase

In addition, there is emerging literature on higher doses being given to patients on infliximab [Stern and Wolfe, 2004; Vollenhoven et al. 2004; Braid et al. 2005]. Dose increase from Stern and Wolfe (shown in Figure 4 below) is included in the base case analysis. Dose rises to 4.5mg/kg at six months and continues to rise at 0.4mg/kg per annum. The model does not permit doses greater than the recommended maximum dose of 10mg/kg. In addition, the mean duration of treatment is such that this upper limit is rarely reached (see section 2.6 above).

Figure 4: Infliximab dose increase (from Stern and Wolfe 2004)



There is much less evidence of dose increase for the other three biologic drugs. Whilst this may be due to the fact that these are newer drugs, the recommendations for dose increases are less flexible than for infliximab. The base case analysis does not include dose increases for any drug other than infliximab. Sensitivity analysis is used to explore the impact of dose changes for etanercept and adalimumab in relation to single biologics only. Simple linear regression was used to estimate the change in dose per month adjusting for concomitant methotrexate use in patients in the NDB. Results are shown in

Table 15 and Table 16 and illustrate that there is no observed increase in the dose of etanercept whilst that associated with adalimumab is slight.

Table 15: Monthly dose of etanercept (mgs)

Number of obs = 8451
F(2, 8448) = 2.98
Prob > F = 0.0507
R-squared = 0.0007
Adj R-squared = 0.0005
Root MSE = 30.274

	Coef.	*Std. Err.*	*t*	*P>|t|*	*[95% Conf.Interval]*	
Time on ETP	-0.037	0.02	-2.44	0.02	-0.07	-0.01
Concomitant MTX	-0.101	0.66	-0.15	0.88	-1.39	1.19
K	194.037	0.71	273.18	0.00	192.64	195.43

Table 16: Monthly dose of adalimumab (mgs)

Number of obs = 3052
F(2, 8448) = 18.10
Prob > F = 0.00
R-squared = 0.0117
Adj R-squared = 0.0111
Root MSE = 26.626

	Coef.	*Std. Err.*	*t*	*P>|t|*	*[95% Conf.Interval]*	
Time on ALB	0.346	0.058	5.93	0.00	0.23	0.46
Concomitant MTX	-0.992	0.972	-1.02	0.31	-2.90	0.91
K	85.432	0.956	89.38	0.00	83.56	87.31

2.12. LIFE TABLES AND MORTALITY

Standard US lifetables [Arias, 2004] were adjusted by standardised mortality rates for patients with RA(Table 17)[Symons et al, 2003].

Table 17: Standardised Mortality Ratios for RA population from Symons et al.

Age	Male	Female
0-24	2	2
25-64	1.6	1.75
65+	1.3	1.5

2.13. DISCOUNTING

Benefits and costs are discounted over the 50yr cycle of the model at a rate of 3% per annum in the base case analysis following recommendations from the US panel on cost effectiveness [Gold et al. 1996]. The impact of 5% and 0% rates is explored in sensitivity analysis.

2.14. NUMBER OF MODEL RUNS REQUIRED

The model is a patient level simulation. Therefore running a probabilistic sensitivity analysis requires stability in both 1st and 2nd order uncertainty. We estimated costs and QALYs for 1000 individuals separately and found that the mean and standard error of the mean to be relatively stable with a minimum of 100 patients for QALYs. 50 patients were sufficient for stability in costs.

We ran the model with 1,000 2nd order Monte Carlo simulations, a total of 100,000 model runs for each evaluation.

3. RESULTS

When calculating cost effectiveness it is important to recognise the appropriate comparator. In the reporting of results that follows, the use of alternative comparators is of interest. Our primary concern is with the additional cost and benefits of etanercept, adalimumab or anakinra (or sequences of these biologics) compared to a strategy of infliximab alone. However, it is also useful to consider a full incremental analysis, that is, each strategy compared to the next most effective alternative that is not dominated[2]. These differences influence both mean cost effectiveness ratios, the probability of a strategy being cost effective (as reflected in CEACs) and EVPI.

In interpreting results, decision makers must consider their Maximum Acceptable Incremental Cost Effectiveness Ratio (MAICER), that is, the value attached to a unit of effectiveness (in this case, a QALY). In CEACs and EVI graphs we plot results for a MAICER range between $0 and $200k per QALY. In the absence of an explicit Medicare threshold we refer to $60k in the narrative purely for illustrative purposes, although $50k to $100k is often cited in the literature [Hirth et al. 2000, Ubel 2003].

Results are presented first considering only the four single biologic strategies (Section 3.1) and second for sequential biologic strategies (Section 3.2). Within each section we present both base case analyses and a number of different scenarios which explore how results change when alternative parameter values are considered. Not all scenarios are included in single and sequential analysis.

3.1. SINGLE BIOLOGIC STRATEGIES

Details of all scenarios run are provided in Appendix 5. A summary of the significant outputs for all scenarios analysed is presented in Table 18 and key scenarios then discussed in more detail.

[2] A strategy is said to be dominated if it both less effective and more costly than an alternative strategy.

Table 18: Single Biologic Model summary cost-effectiveness results for all scenarios.

	ICER compared to IXB ($/QALY)			Probability cost effective at $60k compared to IXB			Global EVPI ($'s) at $60k (excluding AKA)
Analysis	***ETP***	***ALB***	***AKA***	***ETP***	***ALB***	***AKA***	
1	Dominates	Dominates	216573*	1.00	0.99	1.00	1298
2	Dominates	Dominates	577933*	1.00	0.98	1.00	1712
3	Dominates	Dominates	105691*	1.00	1.00	1.00	641
4	Dominates	Dominates	159689*	1.00	1.00	1.00	1058
5	Dominates	Dominates	103502*	0.68	0.70	0.74	14074
6	Dominates	Dominates	116186*	0.73	0.71	0.77	10863
7	Dominates	Dominates	596874*	0.69	0.70	0.92	5416
8	Dominates	Dominates	96925*	1.00	1.00	1.00	690
9	Dominates	Dominates	137978*	1.00	1.00	1.00	1127
10	673156	1363542	86349*	0.00	0.01	0.77	9
11	Dominates	Dominates	218052*	1.00	0.99	1.00	1267
12	Dominates	Dominates	377615*	1.00	0.99	1.00	1259
13	Dominates	Dominates	102810*	0.72	0.64	0.71	5286

* Negative costs and effects

Note: Base case analyses are shaded

3.1.1. Base Case analysis 1 – RCT evidence of effectiveness

Base case analysis 1 consists of EQ5D for health state utilities, meta regression of RCT data for the probability of response at 6 months, NDB is used for HAQ-DI progression after withdrawal from biologic, 3% discount rates, infliximab dose increase and infliximab vials are rounded up to the nearest full vial.

Table 19: Single Biologic Strategies Summary Results – Base Case Analysis

	IXB	ETP	ALB	AKA
Mean Cost	94,029	81,181	79,535	50,608
Se	7,984	5,511	7,730	4,528
Mean QALY	7.64	7.66	7.64	7.44
Se	0.44	0.43	0.44	0.46
ICER (IXB baseline)		Dominates*	Dominates*	216,573
ICER	Dominated*	92,058***	142,726**	
Duration of treatment (yrs)	4.67	5.00	4.97	1.76

* Infliximab is dominated by adalimumab and etanercept
** Compared to anakinra
*** Compared to adalimumab

Figure 5: Scatterplot of costs versus effects from probabilistic analysis

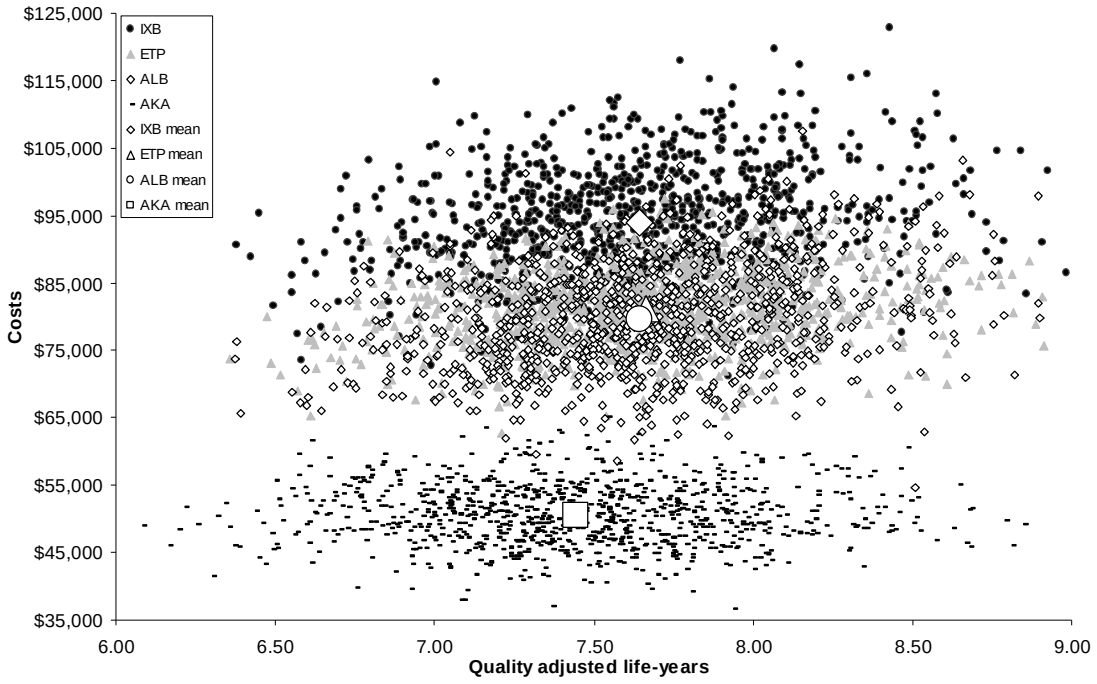


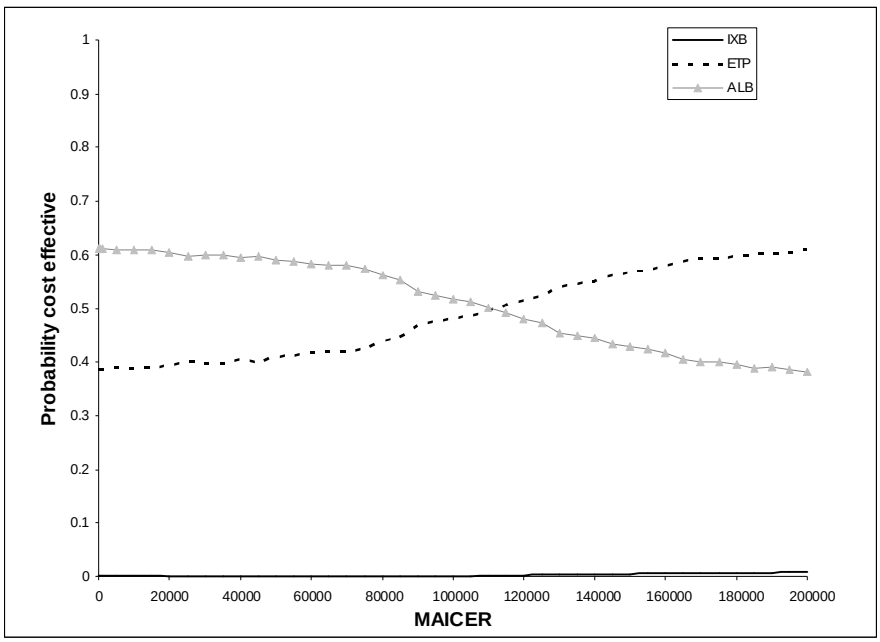
Table 19 reports the mean, discounted costs and QALYs for the four single biologic strategies, using a 50yr time horizon. This is also illustrated in the scatterplot in Figure 5. In this scenario, infliximab is dominated by both etanercept and adalimumab, that is, infliximab is both more costly and less effective when comparing mean costs and effects. However, it should be noted that the difference in effectiveness between the three TNF-α inhibitors is extremely small. The least effective of the four strategies is anakinra, which generates a mean 0.2 of a QALY less per person than infliximab. Whilst the standard errors around these means, and

the scatterplot might seem to indicate that this is not a statistically significant difference, these do not reflect the correlations in the Monte Carlo simulation. In fact, in all simulations of this analysis, anakinra generates the least QALYs since there is both a lower ACR20/50 response rate and a shorter duration of treatment. However, this strategy is also substantially cheaper than all other strategies. Compared to infliximab, the incremental cost effectiveness ratio (ICER) is positive because both mean costs and mean effectiveness are negative. A mean of $217k would be saved for every QALY lost by adopting anakinra rather than infliximab. Under usual decision making thresholds, this would make anakinra the optimal strategy in terms of net benefits. Decision makers may not treat interventions that lie in the south-west quadrant of the cost effectiveness plane (less costly and less effective) in the same way as those which lie to the north east (more costly and more effective). To reflect this, results are displayed which exclude anakinra from the analysis.

Figure 6 displays the cost effectiveness acceptability curves (CEACs). The CEACs plot the proportion of the 1,000 Monte Carlo simulations in which each strategy is cost effective and therefore takes into account the correlations which exist in each run of the simulation. In this case we exclude anakinra and use a range of $0 to $200k as the values a decision maker may be willing to pay per additional QALY gained, also known as the Maximum Acceptable Incremental Cost Effectiveness Ratio (MAICER). Where this willingness to pay is zero, the optimal strategy is adalimumab in 61% of the 1,000 simulations compared to 39% for etanercept. Where the cost effectiveness threshold is higher, the difference between adalimumab and etanercept narrows further until they are equally likely to be cost effective at a threshold of approximately $110k. Infliximab is the optimal strategy in only a handful of simulations even where the willingness to pay for additional health benefits is as high as $200k per QALY.

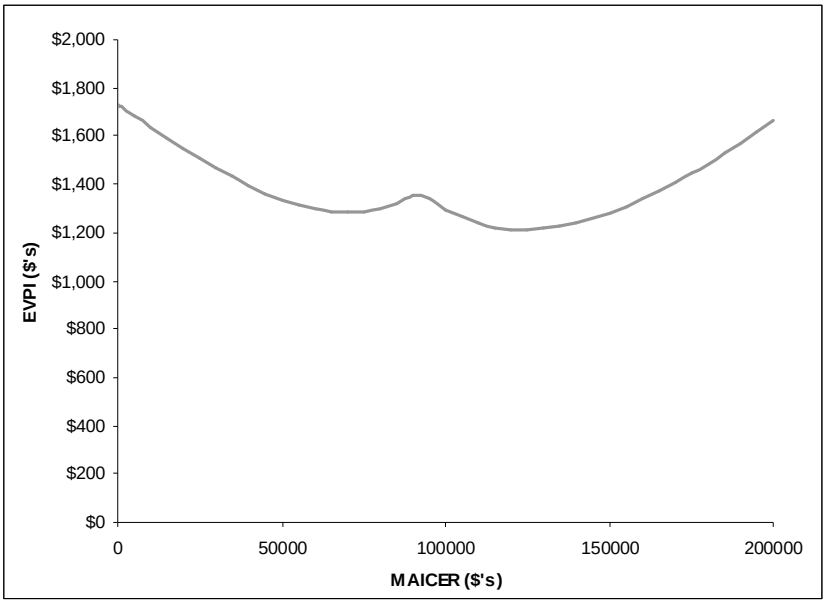
.

Figure 6: Cost effectiveness acceptability curve, single biologic strategies – Base case analysis 1, excluding anakinra



Global EVPI was calculated for each strategy individually compared to infliximab. Below a MAICER of $200k this value was negligible. In the full incremental analysis (including anakinra), EVPI was negligible below a MAICER of $70k. Beyond this point, the probability that etanercept or adalimumab would be preferred to anakinra becomes significant and rises. Therefore EVPI also rises. At $100k the EVPI is $1,000 per person.
Figure 7 displays the EVPI plot calculated excluding anakinra from the analysis. Where MAICER is $60k, EVPI is $1,300 per person.

Figure 7: EVPI plot, single biologic strategies – Base case, incremental analysis, excluding anakinra.



3.1.2. Base Case analysis 2 – NDB evidence of effectiveness

The results for the base case analysis using the NDB for initial response, with all other parameters as in Base Case 1, are shown in Table 20.

Table 20: Single Biologic Strategies Summary Results – Base Case Analysis 2

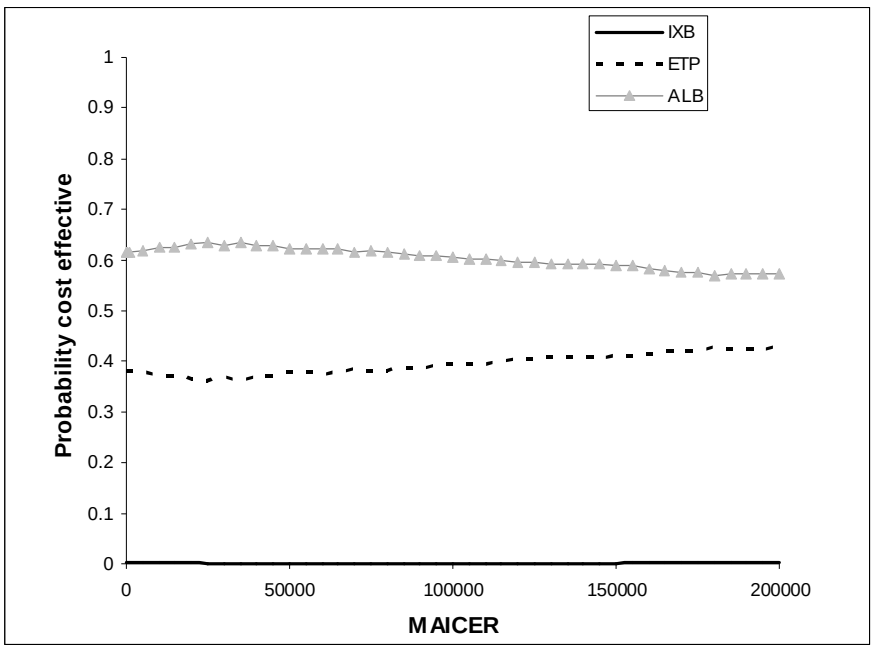
	IXB	ETP	ALB	AKA
Mean Cost	96,017	83,087	81,325	51,534
Se	8,002	5,666	8,275	4,839
Mean QALY	7.43	7.46	7.47	7.36
Se	0.43	0.42	0.43	0.45
ICER (IXB baseline)		Dominates*	Dominates*	577,933
ICER	Dominated*	Dominated**	274,501***	
Duration of treatment (yrs)	4.71	5.04	5.03	1.77

* Infliximab is dominated by adalimumab and etanercept
** Etanercept is dominated by adalimumab
*** Compared to anakinra

The costs generated by each strategy are similar to those in base case analysis 1 but the number of QALYs is substantially reduced for the three TNF-α drugs. This is because of the lower effectiveness of biologics observed in the NDB relative to RCTs.

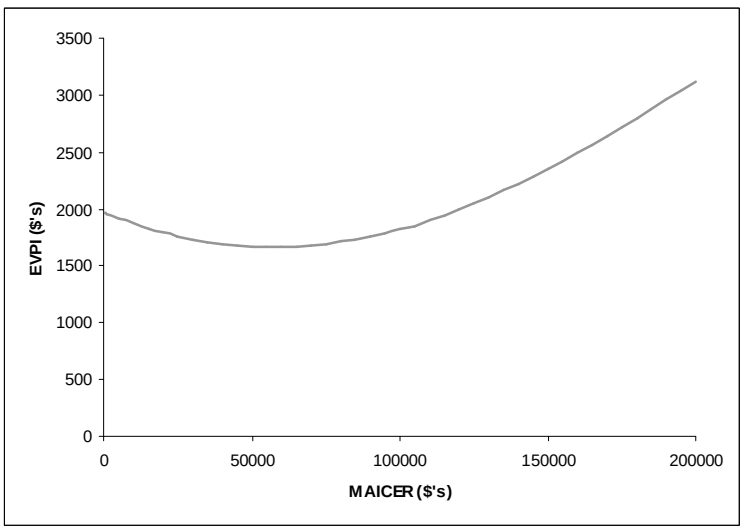
Anakinra remains the least effective of the four drugs. Adalimumab dominates both infliximab and etanercept in terms of mean costs and QALYs, although there is very little difference between etanercept and adalimumab. This is reflected in the CEAC (Figure 8) where the probability that adalimumab is cost effective is above that of etanercept for the entire MAICER range of $0 to $200k. However, the difference in probabilities is relatively small (0.38 for etanercept and 0.62 for adalimumab at $60k).

Figure 8: Cost effectiveness acceptability curve, single biologic strategies – Base case analysis 2, excluding anakinra



EVPI is shown in Figure 9. At $60k per QALY the global EVPI is $1662 per person.

Figure 9: EVPI plot, single biologic strategies – Base case 2, incremental analysis, excluding anakinra.



3.1.3. Sensitivity analyses on the single biologic model

A number of sensitivity analyses were run which explore the impact of alternative assumptions relating to:

i) the use of data from Scott et al. for the rate of HAQ-DI progression post withdrawal from biologic
ii) the use of SF6D based utilities
iii) no dose increase associated with infliximab
iv) no dose increase with infliximab but rounding up to the nearest whole vial
v) Discounting costs and benefits at 5%
vi) Dose changes for adalimumab and etanercept

3.1.3.1. Analysis 3 – As base case 1, HAQ-DI progression from Scott et al.

3.1.3.2. Analysis 4 – As base case 2, HAQ-DI progression from Scott et al.

Minimal differences are observed from the respective base case analyses. All strategies generate slightly lower health benefits in total since disease progression is more rapid after withdrawal from biologic treatment. This also results in slightly higher total costs. However, the differences between strategies are almost identical to those generated by the base case analyses.

3.1.3.3. Analysis 5 – As base case 1, discount rates of 5%.

3.1.3.4. Analysis 6 – As analysis 5, HAQ-DI progression from Scott et al.

3.1.3.5. Analysis 7 – As base case 2, discount rate 5%.

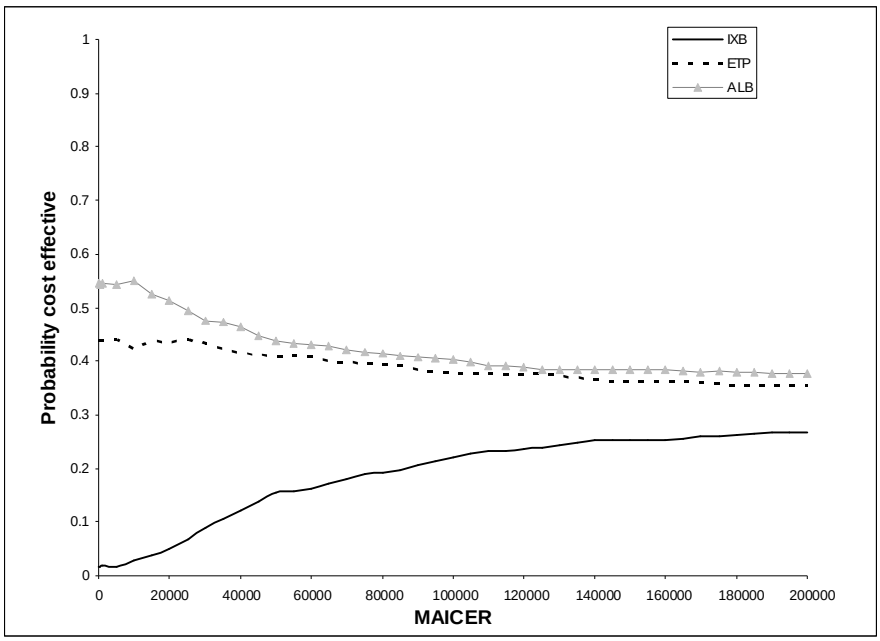
3.1.3.6. Analysis 8 – As analysis 6, discount rate of 0%.

3.1.3.7. Analysis 9 – As analysis 7, HAQ-DI progression from Scott et al., discount rate of 0%.

In previous work in the UK, it has been demonstrated that the discount rates applied to both costs and benefits can be crucially important in the assessment of biologic DMARDs [Brennan et al. 2005]. The discount rate is of particular importance in RA because biologic treatments entail incurring additional costs at the present time in order to secure health benefits that occur both now and in the future. In addition, the duration of biologic treatment differs for each drug, making the discount rate more important.

As specified in US cost effectiveness guidelines [Gold et al. 1996], the impact of 5% and 0% the discount rates are examined. The net effect of a 5% rate is to advantage infliximab compared to the base discount rate. This is because the additional benefits of etanercept and adalimumab which occur in the future are given less weight and the additional costs of infliximab are also downweighted. Infliximab is still more costly than either etanercept or adalimumab but the CEAC reflects greater uncertainty. As Figure 10 illustrates for analysis 5, at MAICER of $60k, the probability that infliximab is the optimal strategy is 0.16 and this rises to 0.22 at $100k.

Figure 10: Cost effectiveness acceptability curve, single biologic strategies – 5% discount rate excluding anakinra



3.1.3.8. Analysis 10 - As base case 1, no IXB dose increase, rounding to full vials

3.1.3.9. Analysis 11 - As base case 1, no rounding to full vials

Analyses 10 and 11 examine the impact of alternative dosing assumptions relating to infliximab. The absence of dose increase for infliximab has a substantial impact on cost effectiveness. Results for analysis 10 exemplify.

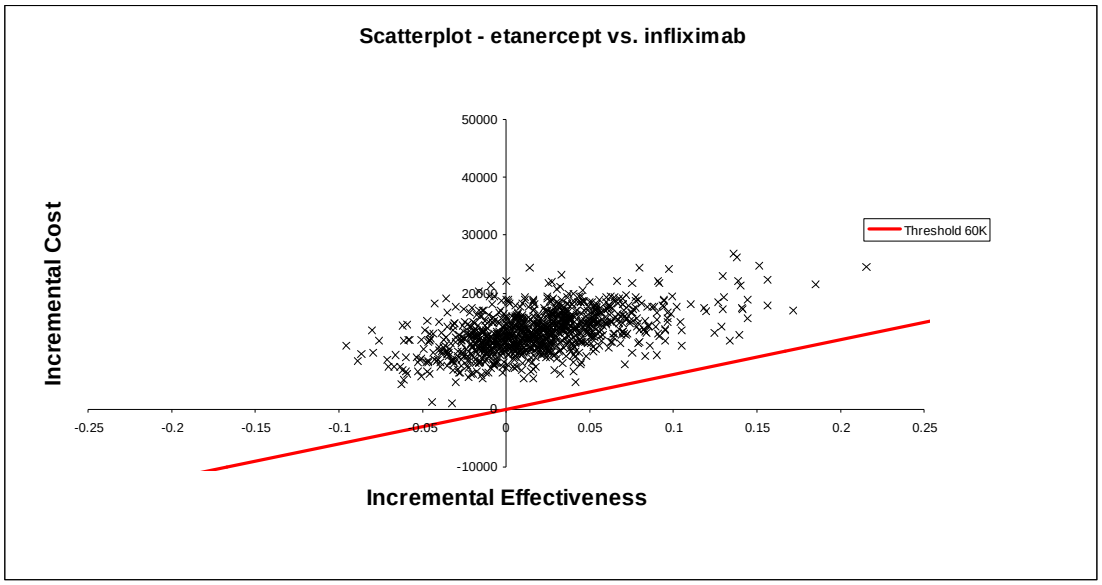
Table 21: Single Biologic Strategies Summary Results – Analysis 10

	IXB	ETP	ALB	AKA
Mean Cost	68,328	81,608	80,281	50,717
se	4,419	5,512	7,995	4,513
Mean QALY	7.64	7.66	7.65	7.44
se	0.43	0.42	0.43	0.46
ICER (IXB baseline)		673,156	1,363,542	86,350
ICER	86,350*	673,156**	121,044***	
Duration of treatment (yrs)	4.69	5.03	5.07	1.76

* Compared to anakinra
** Compared to infliximab
*** Compared to etanercept

Where no dose increase for infliximab is assumed, infliximab generates lower mean costs than either etanercept or adalimumab. In the case of analysis 10, which rounds up the dose to the nearest full vial, infliximab saves in excess of $10k. Since the effects of infliximab are only very slightly lower than etanercept and adalimumab, the resultant cost effectiveness ratios are extremely high. In the case of adalimumab the ICER is in excess of $1m. The scatterplot of etanercept versus infliximab (Figure 11) illustrates that while there is uncertainty in relation to the effectiveness of the two strategies, there is little uncertainty in relation to cost differences. At a MAICER of $60k, etanercept is not cost effective in any simulation.

Figure 11: Scatterplot etanercept vs. infliximab – analysis 10



3.1.3.10. Analysis 12 – As base case 1, SF6D instead of EQ5D for health utilities.

As illustrated in section 2.9, utility is more responsive to changes in HAQ-DI when measured by SF6D than by EQ5D. The results of analysis 12, shown in Table 22 reflect this. Costs are unchanged but each strategy generates at least one QALY less. Furthermore, the difference in QALYs between strategies is reduced resulting in much higher ICERs. In the case of anakinra compared to infliximab, the difference in health benefits is reduced from 0.2 to 0.12 of a QALY, a rise in the ICER from $216k to $378k.

Table 22: Single Biologic Strategies Summary Results – Analysis 12

	IXB	ETP	ALB	AKA
Mean Cost	94,036	81,294	79,301	50,627
se	7,713	5,543	7,903	4,619
Mean QALY	6.56	6.57	6.56	6.44
se	0.34	0.35	0.35	0.35
ICER (IXB baseline)		Dominates***	Dominates***	377,615
ICER	Dominated***	193,801**	249,569*	
Duration of treatment (yrs)	4.68	5.01	4.93	1.76

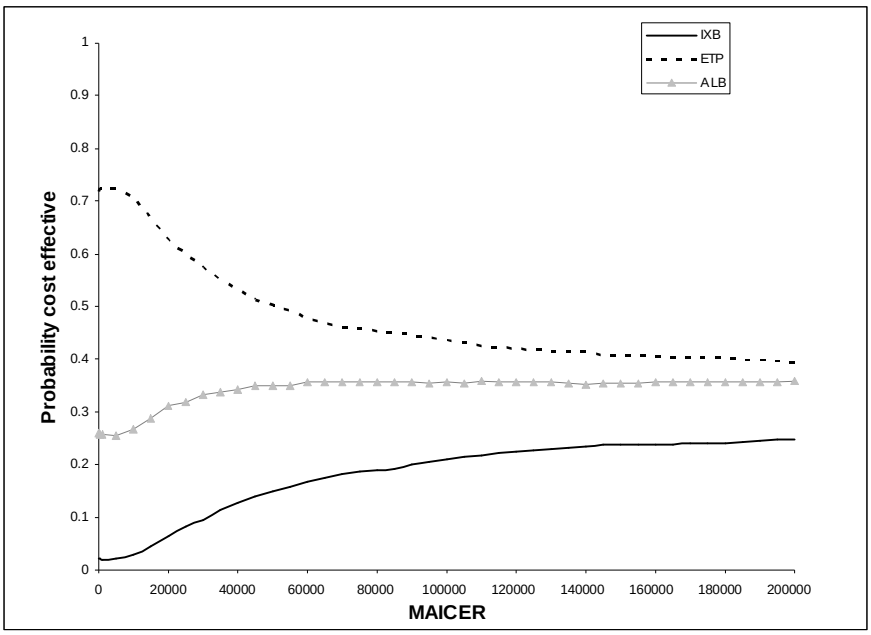
* compared to anakinra
** compared to adalimumab
*** infliximab is dominated by etanercept

3.1.3.11. Analysis 13 – As base case 1, dose increase for etanercept and adalimumab.

The inclusion of dose changes over time for patients on etanercept and adalimumab changes the costs of the adalimumab strategy significantly. An additional cost of approximately $8,000 (10%) is observed. Since there is little evidence of substantial change in the dose of etanercept over time, this strategy is unaffected. The revised

CEAC (Figure 12) illustrates how the probability that etanercept is the optimal strategy is 0.48 compared to 0.36 and 0.17 for adalimumab and infliximab respectively.

Figure 12: Cost effectiveness acceptability curve, single biologic strategies – dose increase for all TNF-a.



3.2. SEQUENTIAL BIOLOGIC STRATEGIES

The three single TNF–α inhibitor therapy strategies were compared to four single-switch and four double-switch strategies as outlined and numbered in 2.2.2. We have not modelled every possible combination of drug switches. As with the single strategy model, a number of different scenarios were examined. Details of all scenarios can be found in Appendix 6. The main outputs of each of these analyses are presented in Table 23. Key scenarios are discussed in detail below.

Table 23: Sequential Biologic Model – Cost per QALY summary for all scenarios ($ 000's)

	Strategy (compared to strategy 1- infliximab)									
Analysis	***ETP***	***ALB***	***IXB, ETP***	***IXB ,ALB***	***ETP, ALB***	***ALB, IXB***	***IXB, ETP, ETP***	***IXB, ALB, ETP***	***ETP, ALB, IXB***	***ETP, IXB, ALB***
1	Dominates	Dominates	253	270	133	297	323	327	326	336
2	Dominates	Dominates	2,275	2,384	425	1,718	46,920	302,732	3,253	7,698
3	Dominates	Dominates	107	108	53	87	128	129	107	115
4	Dominates	Dominates	182	180	80	178	226	227	212	227
5	Dominates	Dominates	115	117	56	91	136	137	110	120
6	Dominates	Dominates	215	210	88	149	262	261	193	221
7	Dominates	Dominates	94	95	47	80	117	117	101	108
8	Dominates	Dominates	154	149	68	119	200	199	162	180
9	687	1,759	256	272	330	313	315	321	346	338
10	236	202	218	212	226	210	265	264	264	268
11	Dominates	Dominates	400	423	208	469	508	518	516	531

Sequential strategies considered

Infliximab
Etanercept
Adalimumab
Infliximab→ etanercept
Infliximab → adalimumab
Etanercept → adalimumab
Adalimumab→ infliximab
Infliximab→ etanercept→ adalimumab
Infliximab→ adalimumab→ etanercept
Etanercept→ adalimumab→ infliximab
Etanercept→ infliximab→ adalimumab

3.2.1. Base case 1

Table 24: Sequential Biologic Strategies Summary Results – Base Case Analysis 1

	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***
Costs	94,414	81,719	80,148	126,974	125,900	112,460	128,515	152,380	152,160	154,136	155,406
QALYs	7.66	7.68	7.67	7.79	7.78	7.79	7.77	7.84	7.84	7.84	7.84
ICER*		Dominates	Dominates	252,850	269,907	133,229	296,872	322,994	327,155	326,419	336,108

*compared to IXB (strategy 1)

In base case analysis 1, each of the three single biologic strategies (1, 2 and 3) generates substantially lower costs than either the two biologic strategies (4 to 7) or the three biologic strategies (8 to 12). Strategy 6 is the lowest cost of the two biologic options, yet is $18k more than infliximab alone (strategy 1). QALY gains from additional biologics are small, in the region of 0.12 for a second biologic and a further 0.06 for a third biologic. Note that while the position of a drug in a sequence is not assumed to affect the probability of response, second and third drugs generate health benefits that are discounted more heavily than those generated by the first. The net benefits of the strategies at a MAICER equal to $60k are displayed in Figure 13.

Figure 13: Net benefits at $60k – Base Case 1

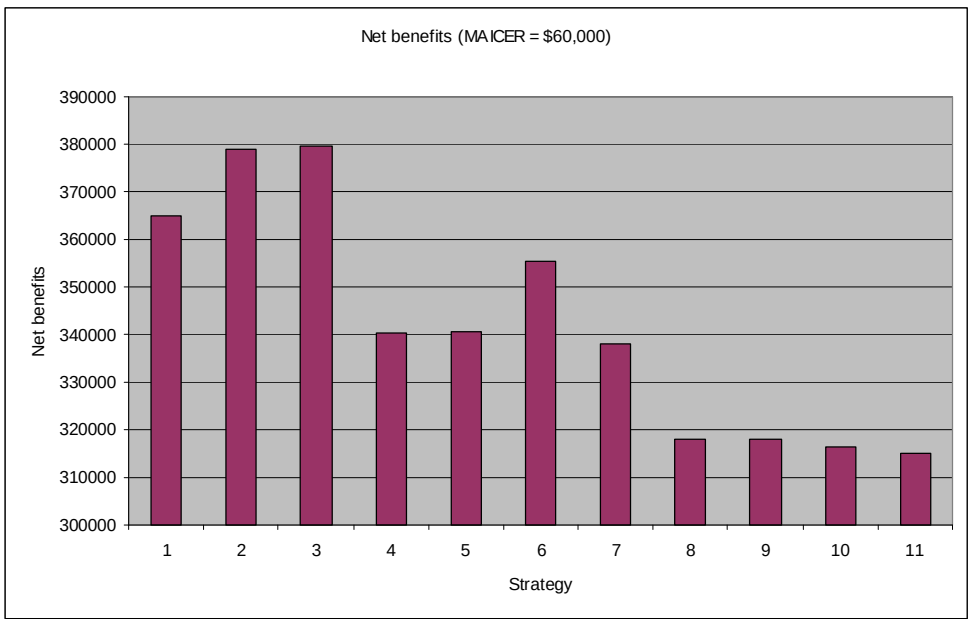
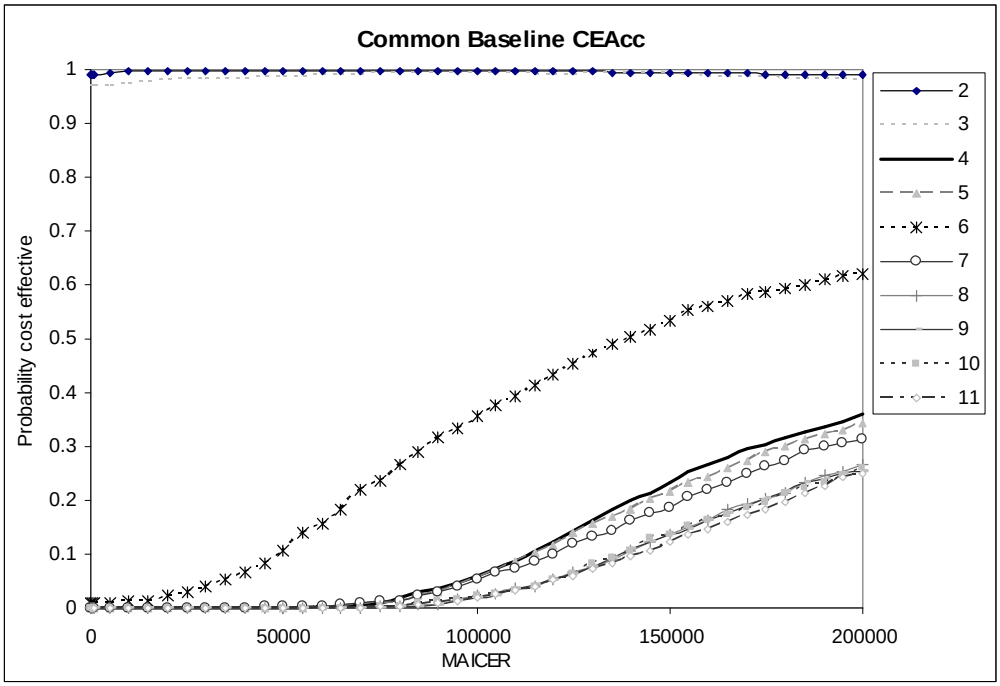


Figure 14: Cost effectiveness acceptability curve, sequential biologic strategies – base case analysis 1, common baseline (infliximab)



The CEACs shown in Figure 14 illustrate that where the MAICER is $60k no sequential strategy has a significant probability of being cost effective compared to infliximab. Where the MAICER is higher the probability rises and becomes significant for strategy 6 (etanercept followed by adalimumab). For example, at $100k per QALY the probability is 0.36.

Global EVPI at $60k per QALY is $846 per person. It should be noted that this figure relates to full incremental analysis between all eleven strategies and not from using infliximab alone as a common baseline. In this scenario, the EVPI figure is driven almost exclusively by the decision uncertainty between scenario 1 (infliximab alone) and strategy 6 (etanercept followed by adalimumab).

3.2.2. Base Case 2

Table 25: Sequential Biologic Strategies Summary Results – Base Case Analysis 2

	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***
Costs	96,043	83,211	81,883	129,673	128,719	115,123	131,556	155,492	155,240	156,945	158,772
QALYs	7.48	7.51	7.51	7.49	7.49	7.52	7.50	7.48	7.48	7.50	7.48
ICER		Dominates	Dominates	2,275k	2,384k	425k	1,718k	46,920k	302,732k	3,253k	7,698k

Table 25 reports the costs and QALYs generated under base case 2 assumptions. Costs and differences in costs are similar to those generated in base case 1. However, the probability of response for any of the three drugs is much lower in this scenario which uses data from the NDB, than base case 1 which draws on RCT data. Consequently, the additional benefits in terms of QALYs of second and third biologics are negligible. ICERs are extremely high in comparison to infliximab alone for all sequential strategies.

No sequential strategy has a probability of being cost effective in comparison to infliximab that exceeds 0.1 at a MAICER of $60k. This probability rises to 0.17 at $100k per QALY for strategy 6.

Global EVPI where the MAICER is $60k is $1,392. In this scenario, much of this value arises because of the uncertainty between strategies 2 and 3 (etanercept versus adalimumab) since there is only a small possibility that any of the sequential strategies is optimal.

3.2.3. Sensitivity analyses on the sequential biologic model

A range of sensitivity analyses were applied to the sequential model.

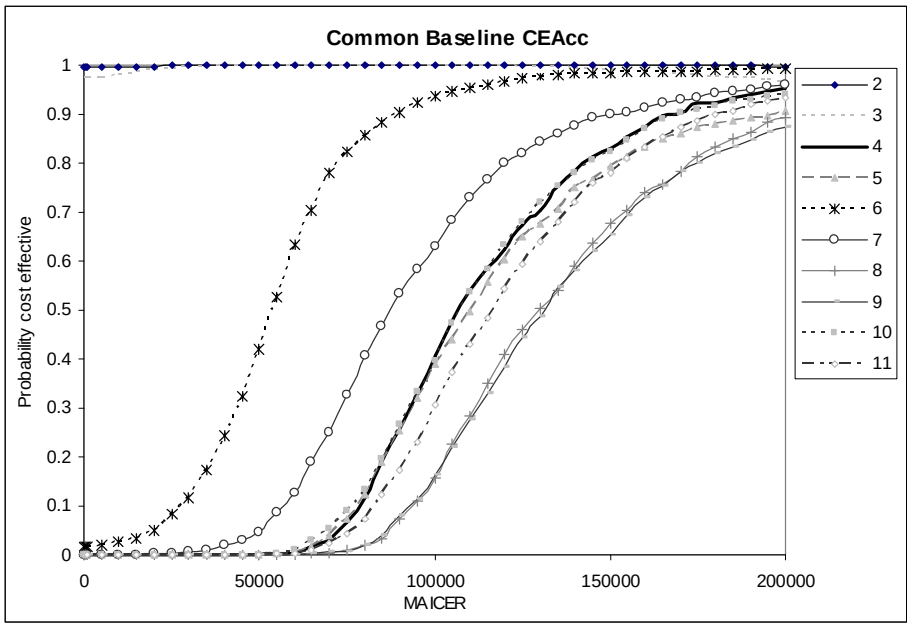
3.2.3.1. Analysis 3 – As base case 1, HAQ-DI progression from Scott et al.

3.2.3.2. Analysis 4 – As base case 2, HAQ-DI progression from Scott et al.

The HAQ-DI progression rate estimated by Scott et al. is substantially greater than the mean rate estimated from the NDB. Therefore, the benefit of second and third biologics is greater than in the base case analyses because the comparator is with patients that are rapidly deteriorating on traditional DMARDs. ICERs are therefore substantially reduced. In both analyses, strategy 6 (etanercept followed by adalimumab) has the lowest ICER compared to infliximab (£53k in analysis 3 and $80k in analysis 4). In neither scenario does the ICER for any three biologic strategy fall below $100k.

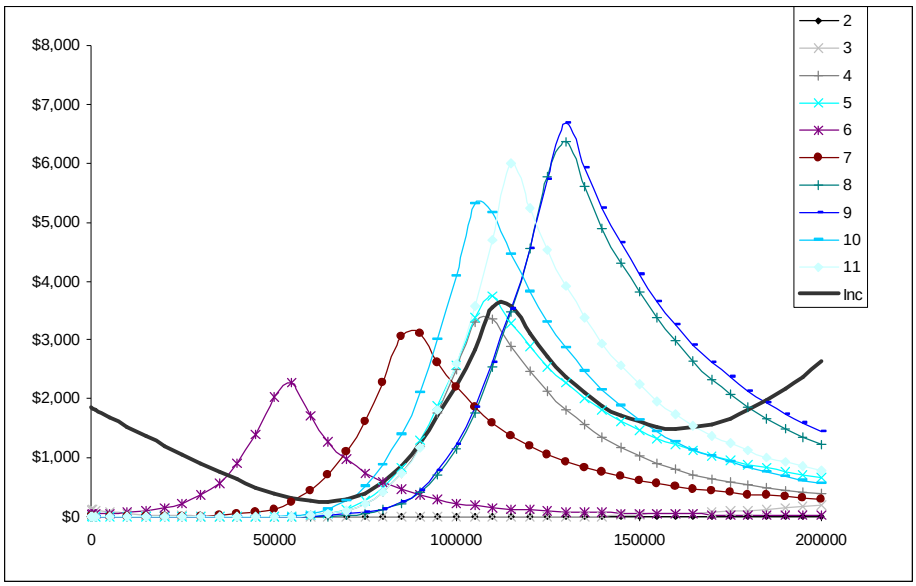
As an illustration, the CEACs for each strategy in analysis 3 compared to infliximab alone are shown in Figure 15. It can be seen that at a MAICER of $60k the probability that any sequential strategy is cost effective remains relatively low. The exception to this is strategy 6 where the probability is 0.63. For all other strategies, this probability rises rapidly if the MAICER is higher. Strategy 7 reaches a probability of 0.5 at approximately $85k.

Figure 15: Cost effectiveness acceptability curve, sequential biologic strategies –analysis 3, common baseline (infliximab)



Global EVPI is plotted in Figure 16 both for each strategy compared to infliximab in isolation and for full incremental analysis in order to demonstrate the relationship between the two. At a MAICER of $60k the value of additional information is low in both the full incremental analysis and the common baseline analysis. There is a peak EVI of $3,558 at $110,000 per QALY in the incremental analysis..

Figure 16: Global EVPI – full incremental and common baseline, analysis 3.



3.2.3.3. Analysis 5 – As base case 1, Scott et al. for HAQ-DI change, 5% discount rate

3.2.3.4. Analysis 6 – As base case 2, Scott et al. for HAQ-DI change, 5% discount rate

3.2.3.5. Analysis 7 – As analysis 5, 0% discount rate

3.2.3.6. Analysis 8 – As analysis 6, 0% discount rate

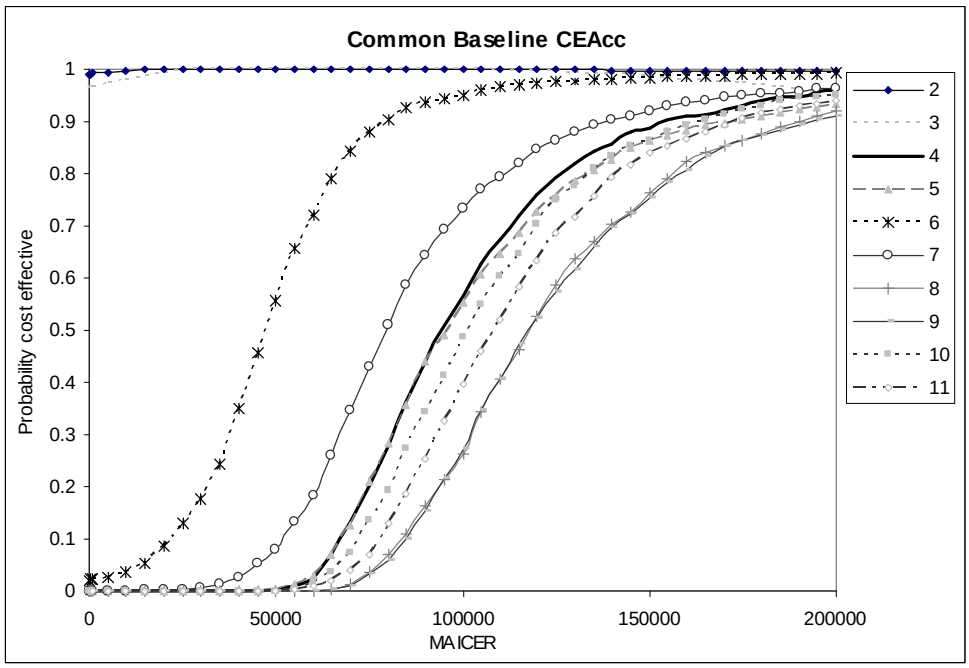
These analyses explore the impact of changes to the discount rate. This is combined with the more optimistic analyses described in analyses 3 and 4, rather than on the base case analyses since the sequential analyses are generally not cost effective irrespective of the discount rate in the base case.

The 5% discount rate for costs and benefits makes most sequential strategies appear less cost effective compared to infliximab alone. There are some exceptions to this in analysis 6 (strategies 7, 10 and 11). These are strategies that comprise etanercept or adalimumab as first biologic rather than infliximab.

The use of a 0% discount rate universally lowers cost effectiveness ratios. In the case of analysis 7, the mean ICERs for each of the two biologic strategies lie below $100k per QALY. The three biologic strategies generate ICERs only slightly higher than $100k per QALY compared to infliximab alone. The most favourable of these is strategy 10, which uses infliximab as the third line biologic drug treatment.

The CEAC for this scenario is illustrated in Figure 17 and is similar to that illustrated for the 3% discount rate (Figure 15). At a MAICER of $60k the probability that strategy 6 is cost effective compared to infliximab is 0.721. The probabilities associated with other strategies are also higher.

Figure 17: Cost effectiveness acceptability curve, sequential biologic strategies – analysis 7, common baseline (infliximab)



3.2.3.7. Analysis 9 – Base case 1, 5% discount rate, no IXB dose increase

3.2.3.8. Analysis 10 – Base case 2, 5% discount rate, no IXB dose increase

These analyses apply a constant 3mg/kg does for infliximab and therefore lowers the cost of all strategies that include infliximab (strategies 1, 4, 5, 7 to 11). Nevertheless, no sequential strategy, including those containing infliximab, generates an ICER below $200k.

3.2.3.9. Analysis 11 – As base case 1, SF6D for health utilities.

As is the case in comparisons of single biologics, the use of SF6D to estimate health state utilities as opposed to EQ5D makes the differences between strategies smaller. Consequently, ICERs for strategies that consist two or three biologics in sequence are higher compared to infliximab alone.

4. DISCUSSION AND CONCLUSIONS

4.1. SUMMARY OF FINDINGS

A cost effectiveness analysis of infliximab versus etanercept, adalimumab and anakinra has been performed from the viewpoint of Medicare as part of the Medicare Replacement Drug Demonstration Program. The model draws on synthesis of randomized controlled trial data as well as analysis of the NDB, one of the richest sources of data on RA in the United States. This synthesis of evidence from apparently diverse sources is crucially important in assessing costs and benefits associated with biologics since they accrue over a much longer time period than can be assessed in a clinical trial.

Two sets of analyses are presented. The first set of analyses assess the cost effectiveness of etanercept, adalimumab and anakinra as alternative treatments to infliximab. Each biologic is considered as a single treatment and upon withdrawal patients are assumed to receive treatment only in the form of traditional, non-biologic DMARDs. The second set of analyses considers alternative strategies consisting of multiple biologics in comparison to infliximab alone.

4.1.1. Single biologic findings

The model estimates that etanercept and adalimumab dominate infliximab in all scenarios except those that maintain a constant dose of 3mg/kg. Differences are predominantly in the cost of treatment as the effectiveness in all TNF antagonists was found to be similar. None of the alternative assumptions explored in sensitivity analyses are sufficient, either alone or in combination, to offset this.

Anakinra is both less effective and less costly than any of the three TNF- α inhibitors. In the model, this is driven both by the lower initial response rate and the shorter duration of treatment for anakinra. In base case analysis 1, anakinra costs $200,000 less per lost QALY, compared to infliximab. In all other scenarios examined, this cost saving ratio is large.

Comparisons between etanercept and adalimumab indicate that both effectiveness and costs are similar in most situations. The emerging evidence on dose changes over time associated with these drugs favours etanercept although more research on this issue is required. While mean cost effectiveness ratios vary substantially depending on the assumptions used, in general there is substantial overlap between the two strategies as demonstrated by probabilistic sensitivity analysis. The consideration of parameter uncertainty is crucially important when considering these results as illustrated in the CEACs.

4.1.2. Sequential biologic findings

The comparisons made in this section of the analysis are effectively a comparison of traditional DMARDs versus biologic therapies in a subgroup of patients – those that have failed a previous DMARD. Whereas in the single biologic strategies the comparison was between one biologic and another, here the strategies differ between having either one or two more biologics after the first withdrawal compared to the

baseline strategy of traditional DMARDs after withdrawal from infliximab. For this reason, the results are substantially different to the single biologic comparisons. In summary, the analysis suggests that it is extremely unlikely to be cost effective to use a second or third biologic drug in patients that have already failed one biologic.

There are several issues that are identified as particularly important in this section of the analysis.

First, the probability that a patient initially responds to any biologic is estimated to be much lower based on data from the NDB than the same probabilities based on RCT data. Consequently, strategies that consist of two or three biologics appear much less cost effective when effectiveness is based on the NDB.

Second, the rate at which costs and benefits are discounted is important because different combinations of biologics entail costs which are incurred early on in order to secure health benefits in the future. Even individual biologic strategies differ in the length of time patients are expected to continue treatment. The recommended discount rate for both costs and benefits is 3% but even small changes to this rate can have profound effects. For example, a QALY in ten years time is worth 34% more where a discount rate of 0% is used in place of 3% (0.74).

Thirdly, the rate at which HAQ-DI (and therefore health utilities) progresses once patients withdraw from biologic therapy is an important determinant of the overall effectiveness of treatment. Even in patients whose HAQ-DI does not improve from biologic therapy, the biologic generates benefits by avoiding a deterioration in health. The rate estimated from the NDB is substantially lower than that which has been estimated from existing studies. This may reflect the fact that previous studies are not measuring the same rate. The required parameter for the cost effectiveness model is specifically, the rate of change in HAQ-DI in patients that have failed a biologic DMARD and are assumed to receive only traditional DMARD therapy. The review by Scott et al. draws exclusively on studies conducted prior to the availability of biologic DMARDs and is a measure of mean progression in patients that receive non biologic DMARDs. These patients comprise those that would never receive a biologic DMARD as well as those that would. Therefore, this rate may not be representative of that experienced by patients after failing a biologic.

Base case analysis 1 suggests that the cost per QALY of all sequential strategies is in excess of $250k. The only exception to this is a strategy of etanercept followed by adalimumab which has a mean cost per QALY of $133k. In base case analysis 2, which uses the NDB to estimate effectiveness, these ICERs are even higher.

Etanercept followed by adalimumab has the lowest cost effectiveness ratio, compared to infliximab alone, of all sequential strategies in every scenario that includes infliximab dose increase.

Where the assumptions that are most favourable to sequential biologic use are made, cost effectiveness ratios remain in excess of $70k per QALY for all strategies other than the two-biologic strategy of etanercept followed by adalimumab. In this case, the cost per QALY is $36k.

The SF6D is less sensitive to changes in HAQ-DI than EQ5D. Using the SF6D reduces the marginal benefit of sequential strategies compared to infliximab and therefore produces even higher ICERs.

4.2. LIMITATIONS OF THE ANALYSIS

There is a substantial difference between the effectiveness of biologic drugs in RCT data and in data from the NDB and this is an important difference particularly in estimating the cost effectiveness of sequential biologic strategies. Wolfe and Michaud [Wolfe and Michaud, 2005] have discussed the reasons why RCT data may overestimate effectiveness compared with observational studies, and provided evidence for these differences. Conversely, it has been argued that this difference is solely due the timing of measurement in the NDB.[Brennan and Bansback, 2004]

The analyses provided here estimate cost effectiveness using both RCT and NDB data on effectiveness. However, the measure of biologic effectiveness used in the model (HAQ-DI response at 6 months) can only be measured in the NDB from a sub sample of patients. The requirement for comparability does not make full use of data available in the NDB and it should be recognised that the resultant samples of patients are particularly small in relation to anakinra and adalimumab. Had all NDB data been, however, overall effectiveness would have been reduced slightly. The hypothesized proper point of reference is discussed in Wolfe and Michaud.[Wolfe and Michaud, 2005]

Any mortality reduction benefits, which might be attributable to TNF inhibitors, are excluded.

The viewpoint of the analysis is restricted to Medicare. This excludes a number of costs important from a societal viewpoint. In particular, the full costs of drugs are not included due to patient co-payments.

Furthermore, the modelled patient cohort is intended to represent the entire RA, Medicare beneficiary population. There is no distinction made Medicare beneficiaries on account of age (over 65yrs) versus disability, or other potentially diverse subgroups.

Not all sequential strategies have been modelled. Our intention was to give preliminary indications of likely cost effectiveness. Whilst we focus on strategy 6 in particular (etanercept followed by adalimumab) our expectation is that adalimumab followed by etanercept would generate extremely similar results.

We have made two strong assumptions based on limited data:

i) that patients experience a worsening HAQ-DI equivalent to the initial improvement in HAQ-DI at first response at the time they withdraw from a biologic.
ii) That the probability of response to a biologic is independent of its position in a sequence.

Both assumptions may warrant further investigation. It should be recognised that the modelling of sequential therapy is substantially affected by this second assumption.

Nevertheless, the ICERs for second or third biologic use are relatively high in most scenarios despite this optimistic assumption.

4.3. IMPLICATIONS FOR FURTHER RESEARCH

There are additional analyses of the NDB that may, together with alterations to the cost effectiveness model, permit an analysis of cost effectiveness that makes full use of data on effectiveness. These estimates are difficult due to the fact that NDB observation points do not necessarily coincide with the start of biologic treatment.

In addition, we have not conducted analyses of the NDB to identify the probability of response to second and third biologics.

When considering second and third biologics, the cost effectiveness of alternative rules for stopping treatments may be important. For instance, the current UK NHS NICE guidelines specify that patients should be at least a moderate responder at 3 months to remain on treatment, where response is measured in terms of EULAR Disease Activity Score (DAS28).[NICE, 2002] Simple modifications to the cost effectiveness models used in this analysis would permit alternative HAQ-DI based stopping rules to be explored. Similarly, the cost effectiveness of biologic drug strategies in different subgroups of the Medicare population, in particular those over 65 years and the disabled under 65 years, might be investigated in future research.

5. REFERENCES

Abbott Laboratories. Humira Prescribing Information Sheet. http://www.rxabbott.com/pdf/humira.pdf [accessed 1st December 2005]

Agency for Healthcare Research and Quality. U.S. Valuation of the EuroQol EQ-5D Health States. February 2005. http://www.ahrq.gov/rice/EQ5Dproj.htm

American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the Management of Rheumatoid Arthritis. 2002 Update. Arthritis Rheum 2002;46:328-46.

Arias E. United States life tables, 2002. National vital statistics reports; vol 53 no 6. Hyattsville, Maryland: National Center for Health Statistics. 2004. http://www.cdc.gov/nchs/data/nvsr/nvsr53/nvsr53_06.pdf [accessed 1st December 2005]

Bansback N, Brennan A, Ghatnekar O. The cost effectiveness of adalimumab in the treatment of moderate to severe rheumatoid arthritis patients in Sweden Ann Rheum Dis Published Online First November 18th 2004 doi: 10.1136/ard.2004.027565

[Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. J Health Serv Res Policy. 2004;9(2):110-8

Braid M, Tandon N, Ziskand M. Infliximab Dosing and Cost Analysis of Medicare Rheumatoid Arthritis Patients. Arthritis Rheum 2004;50 Suppl 9: S695

Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics 2002; 21:271-292.

Brennan A, Bansback N. Re: Wolfe et al. Do rheumatology cost-effectiveness analyses make sense? Rheumatology. 2004;43(5):677-8

Brennan A, Bansback NJ, Reynolds A, et al. Modeling the cost effectiveness of etanercept in adults with rheumatoid arthritis in the UK. Rheumatology 2004; 43: 62-72

Brennan, A., Bansback, N., and Nixon, R. (2005) Modelling the cost effectiveness of tnf-α inhibitors in the management of rheumatoid arthritis: results from the British society for rheumatology biologics registry.

Bresnihan B; Alvaro-Gracia JM; Cobby M; Doherty M; Domljan Z; Emery P; Nuki G; Pavelka K; Rau R; Rozman B; Watt I; Williams B; Aitchison R; McCabe D; Musikic P. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41(12):2196-204.

Briggs A. Handling uncertainty in economic evaluation and presenting the results. pp172-214 in Drummond M. McGuire A. (Eds.) Economic evaluation in health care: merging theory with practice. OHE / Oxford University Press, Oxford 2001

Callahan LF. The burden of rheumatoid arthritis: facts and figures. J Rheumatol Suppl 1998; 53: 8-12

Centocor Inc. Remicade Prescribing Information Sheet. http://www.remicade.com/pdf/HCP_PPI.pdf [accessed 1st December 2005]

Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, Fry-Smith A, Burls A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost effectiveness. West Midlands HTA Collaboration, October 2005. http://www.nice.org.uk/page.aspx?o=290924 [accessed 8th August 2006]

Choi HK, Hernan MA, Seeger SD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: A prospective study. Lancet 2002;359:1173-1177.

Drummond M F, O'Brien B J, Stoddart G L, Torrance G W. Methods for the economic evaluation of health care programmes. Oxford University Press, 2005.

Felli C,.Hazen GB. Sensitivity analysis and the expected value of perfect information. Medical Decision Making 1998;18:95-109.

Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A meta-analysis of published clinical trials. Arthritis Rheum 1992;35:1117-25.

Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 2001;10:779-89.

Galindo-Rodriguez G, Avina-Zubieta JA, Russell AS, Suarez-Almazor ME. Disappointing longterm results with disease modifying antirheumatic drugs. A practice based study. J Rheumatol 1999;26:2337-43.

Gold MR, Siegel JE. Russell LB, Weinstein MC. Cost effectiveness in health and medicine. New York: OUP, 1996.

Greene WH. Econometric Analysis, 4th edition. Prentice Hall Inc., New Jersey.

Hirth RA, Chernew ME, Miller E, Fendrick M, Weissert WG. Willingness to pay for a Quality Adjusted Life year: In search of a standard. Medical Decision Making 2000;20:332-342.

Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2002;6(21).

Kobelt G, Jonsson L, Young A, et al. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology 2003; 42: 326-35

Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis 2004; 63: 4-10

Law, A.M., and Kelton, W.D. (2000) Simulation Modelling and Analysis, third edition, McGraw-Hill;Singapore.

Lawrence, R., Helmick, C.G., Arnett, F.C., Deyo, R,A., Felson, D.T., Giannini, E,H., et al. (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States, *Arthritis and Rheumatism*, Vol.41(5):778-799.

Maini R; St Clair EW; Breedveld F; Furst D; Kalden J; Weisman M; Smolen J; Emery P; Harriman G; Feldmann M; Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.

Moreland LW; Baumgartner SW; Schiff MH; Tindall EA; Fleischmann RM; Weaver AL; Ettlinger RE; Cohen S; Koopman WJ; Mohler K; Widmer MB; Blosch CM. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337(3):141-7.

Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7527 patients. Arthritis Rheum 2003; 48:2750-62

Murray MP. [2006] Econometrics. A Modern Introduction. 2006, Pearson Education Inc, Boston.

National Institute for Clinical Excellence. Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. Technology Appraisal Guidance – No. 36. March 2002

Pincus T, Callahan LF. The 'side effects' of rheumatoid arthritis: joint destruction, disability, and early mortality. Br J Rheumatol 1993; 32 Suppl. 1: 28-37

Scott DL, Garrood T. Quality of life measures: use and abuse. Best Pract Res Clin Rheumatol. 2000;14(4):663-687

Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J, Hieke K. The links between joint damage and disability in rheumatoid arthritis. Rheumatology 2000;39:122-132.

Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. Journal of Rheumatology 2004:31:1538-45.

Symmons D, Mathers C, Pfleger B, World Health Organization: The global burden of rheumatoid arthritis in the year 2000. [http://www3.who.int/whosis/menu.cfm?path=evidence,burden,burden_gbd2000docs &language=english] 2003.

Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med 163: 1637–1641, 2003

van Vollenhoven RF, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. Annals of the Rheumatic Diseases 2004; 63:426-430

Weinblatt, M. E, Keystone, E. C, Furst, D. E, Moreland, L. W, Weisman, M. H, Birbara, C. A, Teoh, L. A, Fischkoff, S. A, Chartash, E. K. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48(1):35-45.

Wolfe, F, and Michaud, K. A brief introduction to the National Data Bank for Rheumatic Diseases. Clinical and Experimental Rheumatology 2005; 23(5) supp 39: S168 -S171

Wolfe, F, and Michaud, K. Toward an epidemiology of RA outcome with respect to treatment: randomized controlled trials overestimate treatment response and effectiveness. Rheumatology 2005; 44(supp 4):iv18-iv22.

Wolfe F, Michaud K, Gefeller O, et al. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003; 48: 1530-42

Wolfe F, Michaud K, Choi HK, Williams R. Household Income and Earnings Losses Among 6,396 Persons with Rheumatoid Arthritis. The Journal of Rheumatology 2005;32:1875-83.

Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum 2001; 44: 2746-9

Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. Am J Med 2002; 113: 400-8

Yelin E, Callahan LF, for the National Arthritis Data Work Group. The economic cost and social psychological impact of musculoskeletal conditions. Arthritis Rheum 1995; 38: 1351-6

6. APPENDICES

Appendix 1: Previous research and conflict of interest statement

Allan Wailoo declares no conflict of interest

Richard Nixon declares no conflict of interest.

At the time of the analysis, Alan Brennan (AB) and Nick Bansback (NB) had received previous research funding from 3 companies for work in RA(see below). AB and NB have received sponsorship to attend academic conferences from 2 companies.

Colleagues in ScHARR are completing a separate analysis for 1 company.
Other ongoing work does not represent a conflict of interest.

AB and NB have completed the following projects in the area of biologics in RA:

1. Modeling cost effectiveness of etanercept in the UK. Funded by Wyeth. Project completed 2001.
2. Modeling cost effectiveness of adalimumab in 10 countries including the US. Funded by Abbott. Project completed June 2004
3. Cost effectiveness of a genetic test to detect responders to anakinra. Funded by Interleukin Genetics. Completed 2002.
4. Modeling the cost effectiveness of TNF-αinhibitors in the UK. Funded by the British Society of Rheumatologists. Completed May 2005.

AB and NB have also been involved in projects concerning biologics in other indications:

5. Cost effectiveness of etanercept in the treatment for Psoriatic Arthritis. Funded by Wyeth. Completed

AB , NB and RN have one further projects related to RA.

6. A methodology project examining methods for optimising clinical trial development decisions, using RA therapies as one case study. This is funded by a company, which does not have a biologic product in the RA market.

NB has commenced work on one further project relating to RA.

7. A joint VA/Canadian Institute for Health Research project studying a TNF antagonist for Rheumatoid Arthritis, and funding from Abbott Laboratories to analyze determinants of quality of life in psoriatic arthritis.

Other University of Sheffield staff
Cost effectiveness of etanercept in the treatment of Ankylosing Spondylitis. Funded by Wyeth, completed 2005.

The NDB has received research funding from Abbott, Amgen, Bristol-Myers-Squibb, Centocor and Sanofi-Aventis pharmaceutical companies.

Appendix 2: Variance covariance matrices

a) Logit probability of ACR20 response - MTX

	MTX	disease duration	Baseline HAQ
MTX	0.0505	0.0007	0.0008
disease duration	0.0007	0.0023	-0.0100
Baseline HAQ	0.0008	-0.0100	2.7022

b) Logit probability of ACR50 response - MTX

	MTX	disease duration	Baseline HAQ
MTX	0.0500	0.0021	-0.0198
disease duration	0.0021	0.0021	-0.0155
Baseline HAQ	-0.0198	-0.0155	2.4520

c) Log odds ACR20 response

	AKA	ATP	IXB	ALB	Disease duration	Baseline HAQ
AKA	0.0363	-0.0017	-0.0021	-0.0014	-0.0002	0.0435
ATP	-0.0017	0.0394	0.0002	0.0054	-0.0001	-0.0229
IXB	-0.0021	0.0002	0.0410	-0.0008	0.0017	-0.0229
ALB	-0.0014	0.0054	-0.0008	0.0225	-0.0003	-0.0148
Disease duration	-0.0002	-0.0001	0.0017	-0.0003	0.0005	-0.0042
Baseline HAQ	0.0435	-0.0229	-0.0229	-0.0148	-0.0042	0.4100

d) Log odds ACR50 response

	AKA	ATP	IXB	ALB	Disease duration	Baseline HAQ
AKA	0.0638	-0.0046	0.0010	0.0010	0.0000	0.0601
ATP	-0.0046	0.0568	0.0022	0.0108	0.0005	-0.0562
IXB	0.0010	0.0022	0.0538	0.0014	0.0030	-0.0364
ALB	0.0010	0.0108	0.0014	0.0300	0.0003	-0.0163
Disease duration	0.0000	0.0005	0.0030	0.0003	0.0007	-0.0076
Baseline HAQ	0.0601	-0.0562	-0.0364	-0.0163	-0.0076	0.6096

e) Proportional odds cumulative Logit model for predicting type of response

	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8 - IXB	x_8 - AKA	x_8 - ALB	$x_{9 - over\ 65}$	$x_{9 - disability}$	x_{10}	x_{11}	x_{12}	a_1	a_2
x_1	0.0003																
x_2	0.0000	0.0002															
x_3	-0.0001	0.0000	0.0061														
x_4	-0.0002	-0.0002	-0.0030	0.0527													
x_5	-0.0005	-0.0001	0.0008	0.0154	0.1077												
x_6	0.0000	-0.0003	0.0008	0.0039	0.0000	0.1405											
x_7	0.0001	-0.0002	0.0001	-0.0013	0.0002	-0.0006	0.0060										
x_8 - IXB	-0.0005	0.0003	0.0001	-0.0008	0.0030	-0.0192	0.0002	0.0755									
x_8 - AKA	-0.0005	0.0006	0.0004	-0.0066	-0.0043	-0.0048	0.0001	0.0315	0.4877								
x_8 - ALB	-0.0006	-0.0004	-0.0015	0.0049	0.0094	0.0034	0.0019	0.0348	0.0270	0.4005							
$x_{9 - over\ 65}$	-0.0005	-0.0002	-0.0016	-0.0162	-0.0065	-0.0082	-0.0012	-0.0047	0.0274	-0.0177	0.3834						
$x_{9 - disability}$	-0.0050	0.0000	0.0004	0.0115	0.0104	0.0077	0.0008	-0.0070	0.0179	0.0024	0.0509	0.1806					
x_{10}	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000				
x_{11}	0.0001	0.0000	-0.0001	0.0015	-0.0022	0.0014	0.0001	-0.0016	0.0033	-0.0017	-0.0029	-0.0008	0.0000	0.0037			
x_{12}	-0.0004	0.0005	-0.0035	0.0000	-0.0083	-0.0022	-0.0030	0.0047	0.0030	0.0685	-0.0121	-0.0078	0.0000	0.0009	0.2025		
a_1	0.0131	0.0000	0.0002	0.0794	-0.0164	0.1357	0.0192	-0.0257	0.0571	0.0456	-0.0433	-0.2021	0.0000	0.0508	0.1567	1.8296	
a_2	0.0130	-0.0001	-0.0004	0.0776	-0.0153	0.1363	0.0192	-0.0272	0.0556	0.0449	-0.0431	-0.1999	0.0000	0.0505	0.1512	1.8100	1.8187

f) Multivariate regression model to predict HAQ-DI 6 months after starting biologic treatment

	x_1	x_2	x_3	x_4	x_5	x_6	x_7	$x_{9\text{ - over 65}}$	$x_{9\text{ - disability}}$	x_{10}	x_{11}	x_{12}	x_{13}	x_{13}	constant
x_1	0.0000														
x_2	0.0000	0.0000													
x_3	0.0000	0.0000	0.0002												
x_4	0.0000	0.0000	-0.0001	0.0008											
x_5	0.0000	0.0000	0.0001	0.0004	0.0051										
x_6	0.0000	0.0000	0.0001	0.0001	0.0001	0.0054									
x_7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002								
$x_{9\text{ - over 65}}$	0.0000	0.0000	0.0000	-0.0004	-0.0003	-0.0004	-0.0001	0.0134							
$x_{9\text{ - disability}}$	-0.0002	0.0000	0.0000	0.0002	0.0005	0.0002	0.0000	0.0019	0.0079						
x_{10}	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000					
x_{11}	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	-0.0001	-0.0001	0.0000	0.0002				
x_{12}	0.0000	0.0000	-0.0002	0.0000	-0.0004	-0.0001	-0.0001	-0.0003	-0.0003	0.0000	0.0000	0.0108			
x_{13}	0.0000	0.0000	0.0001	-0.0001	0.0001	-0.0003	0.0000	-0.0003	-0.0004	0.0000	0.0000	0.0003	0.0051		
x_{13}	0.0000	0.0000	0.0001	0.0005	-0.0004	0.0002	0.0000	0.0002	0.0000	0.0000	0.0001	0.0013	0.0011	0.0093	
constant	-0.0007	0.0000	-0.0003	-0.0002	0.0013	-0.0041	-0.0010	0.0004	0.0112	0.0000	-0.0021	-0.0085	-0.0017	-0.0042	0.0823

g) Post 6 month Improvement in HAQ-DI on Biologic Therapy

	t	tx_1	tx_2	tx_3	tx_4	tx_5	tx_6	tx_7	$tx_{9 - over\ 65}$	$tx_{9 - disability}$	tx_{10}	tx_{11}	tx_{12}
t	0.0001												
tx_1	0.0000	0.0000											
tx_2	0.0000	0.0000	0.0000										
tx_3	0.0000	0.0000	0.0000	0.0000									
tx_4	0.0000	0.0000	0.0000	0.0000	0.0000								
tx_5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000							
tx_6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000						
tx_7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000					
$tx_{9 - over\ 65}$	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000				
$tx_{9 - disability}$	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000			
tx_{10}	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000		
tx_{11}	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	
tx_{12}	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

h) Multivariate Weibull survival analysis to predict time on 1st biologic treatment

	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8 - IXB	x_8 - AKA	x_8 - ALB	x_{9} - *over 65*	x_{9} - *disability*	x_{10}	x_{11}	x_{12}	*K*	*Ln p*
x_1	0.00002																
x_2	0.00000	0.00001															
x_3	0.00000	0.00000	0.00025														
x_4	-0.00001	-0.00001	-0.00017	0.00230													
x_5	-0.00003	0.00001	-0.00001	0.00073	0.00613												
x_6	0.00000	0.00001	0.00012	-0.00003	0.00005	0.00669											
x_7	0.00000	-0.00001	-0.00002	-0.00010	0.00005	-0.00009	0.00032										
x_8 - IXB	-0.00002	0.00000	-0.00003	-0.00007	-0.00011	-0.00097	0.00005	0.00410									
x_8 - AKA	0.00000	-0.00003	0.00003	-0.00003	-0.00026	-0.00056	0.00006	0.00216	0.02175								
x_8 - ALB	-0.00003	-0.00002	-0.00017	0.00057	0.00027	-0.00086	0.00015	0.00221	0.00240	0.03627							
x_{9} - *over 65*	-0.00002	-0.00003	-0.00008	-0.00077	-0.00039	-0.00028	-0.00013	-0.00009	0.00053	-0.00098	0.01565						
x_{9} - *disability*	-0.00030	-0.00001	0.00001	0.00012	0.00015	0.00007	0.00005	-0.00078	-0.00031	-0.00006	0.00261	0.01021					
x_{10}	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000				
x_{11}	0.00000	0.00000	0.00000	0.00005	0.00000	-0.00001	-0.00001	0.00002	0.00013	0.00002	-0.00003	-0.00007	0.00000	0.00018			
x_{12}	-0.00002	0.00001	-0.00014	0.00028	-0.00009	-0.00047	-0.00005	0.00005	0.00008	0.00090	0.00004	-0.00046	0.00000	0.00005	0.01115		
K	-0.00086	0.00001	-0.00019	-0.00286	-0.00015	-0.00463	-0.00060	-0.00055	-0.00430	-0.00312	0.00141	0.01505	0.00000	-0.00243	-0.00831	0.10460	
Ln p	0.00000	0.00000	0.00002	-0.00002	-0.00001	-0.00002	-0.00001	0.00006	0.00039	0.00051	0.00000	-0.00002	0.00000	0.00000	-0.00005	-0.00201	0.00059

g) Multivariate regression model to predict HAQ-DI after withdrawal from biologic therapy

	t	tx_1	tx_2	tx_3	tx_4	tx_5	tx_6	tx_7	$tx_{9\text{ - over 65}}$	$tx_{9\text{ - disability}}$	tx_{10}	tx_{11}	tx_{12}
t	0.00035												
tx_1	0.00000	0.00000											
tx_2	0.00000	0.00000	0.00000										
tx_3	0.00000	0.00000	0.00000	0.00000									
tx_4	0.00001	0.00000	0.00000	0.00000	0.00000								
tx_5	0.00003	0.00000	0.00000	0.00000	0.00000	0.00004							
tx_6	-0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001						
tx_7	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000					
$tx_{9\text{ - over 65}}$	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001				
$tx_{9\text{ - disability}}$	0.00004	0.00000	0.00000	0.00000	0.00000	0.00001	0.00000	0.00000	0.00001	0.00003			
tx_{10}	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000		
tx_{11}	-0.00001	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	
tx_{12}	-0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00002

h) Relationship between HAQ-DI and EQ5D

	x_1	x_2	x_4	x_5	x_7	x_{13}	K
x_1	0.00000						
x_2	0.00000	0.00000					
x_4	0.00000	0.00000	0.00010				
x_5	0.00000	0.00000	0.00001	0.00014			
x_7	0.00000	0.00000	0.00000	0.00000	0.00001		
x_{13}	0.00000	0.00000	-0.00007	0.00002	0.00000	0.00011	
K	-0.00001	0.00000	-0.00002	-0.00003	-0.00002	-0.00003	0.00069

i) Relationship between HAQ-DI and SF6D

	x_1	x_2	x_4	x_5	x_7	x_{13}	K
x_1	0.00000						
x_2	0.00000	0.00000					
x_4	0.00000	0.00000	0.00010				
x_5	0.00000	0.00000	0.00002	0.00032			
x_7	0.00000	0.00000	0.00000	0.00000	0.00001		
x_{13}	0.00000	0.00000	-0.00003	0.00001	0.00000	0.00011	
K	-0.00002	0.00000	-0.00007	-0.00004	-0.00004	-0.00010	0.00133

j) Medicare resource use by HAQ-DI

	x_1	x_2	x_3	x_4	x_{13}	x_5	x_6	x_7	$x_{8\text{ - ETP}}$	$x_{8\text{ - IXB}}$	$x_{8\text{ - AKA}}$	$x_{8\text{ - ALB}}$	x_{10}	x_{11}	x_{12}	K
x_1	0.69															
x_2	-0.13	1.51														
x_3	-1.68	-0.08	94.56													
x_4	2.78	4.12	-1.62	674.35												
x_{13}	-5.55	-6.43	-104.43	-476.56	910.07											
x_5	-7.09	-1.85	-36.58	75.48	34.10	1314.55										
x_6	-0.79	7.21	29.35	51.29	64.16	-35.89	1293.68									
x_7	0.18	-1.90	-4.06	-64.09	-0.83	-18.38	-153.65	97.92								
$x_{8\text{ - ETP}}$	2.10	2.13	-35.82	27.76	-118.33	-50.45	98.63	-95.73	3704.24							
$x_{8\text{ - IXB}}$	0.09	3.83	22.41	-76.25	-21.48	-147.61	-25.27	-5.50	177.85	2233.13						
$x_{8\text{ - AKA}}$	19.33	5.33	26.22	-197.12	-618.11	-1053.77	-444.61	186.82	279.87	384.15	446567					
$x_{8\text{ - ALB}}$	10.09	3.38	40.99	-207.45	-66.61	-149.15	-174.44	106.14	-6.49	107.75	482.27	1252.35				
x_{10}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.01	0.00			
x_{11}	1.23	0.54	2.02	-6.06	9.24	-8.15	19.23	0.22	-3.53	30.76	113.14	-52.30	0.00	35.80		
x_{12}	-0.03	-4.82	-14.30	-22.33	121.68	-32.85	138.30	-23.04	-62.47	85.34	-558.68	-125.30	0.00	-26.59	2262.13	
K	-45.58	-15.42	-3.39	-309.71	64.12	386.29	-1476.87	40.70	98.72	-558.56	-1406.20	-93.67	0.00	-528.92	-1843.66	13155

Appendix 3: Review of effectiveness of biologic DMARDs.

See separate document

Appendix 4: Meta-analysis of RCT data.

See separate document

Appendix 5: Single biologic sensitivity analyses

		MODEL OPTIONS						
		Health state utilities: EQ5D vs. SF6D	**Response at 6 months: RCTs vs. NDB**	**HAQ change after withdrawal: NDB vs. Scott**	**Discount rates**	**IXB dose increase**	**IXB round up to full vial**	**ALB/ETP dose increase**
ANALYSIS NUMBER	1	EQ5D	RCT	NDB	3%	Yes	Yes	No
	2	EQ5D	NDB	NDB	3%	Yes	Yes	No
	3	EQ5D	RCT	Scott	3%	Yes	Yes	No
	4	EQ5D	NDB	Scott	3%	Yes	Yes	No
	5	EQ5D	RCT	NDB	5%	Yes	Yes	No
	6	EQ5D	RCT	Scott	5%	Yes	Yes	No
	7	EQ5D	NDB	NDB	5%	Yes	Yes	No
	8	EQ5D	RCT	Scott	0%	Yes	Yes	No
	9	EQ5D	NDB	Scott	0%	Yes	Yes	No
	10	EQ5D	RCT	NDB	3%,	No	Yes	No
	11	EQ5D	RCT	NDB	3%	Yes	No	No
	12	SF6D	RCT	Scott	3%	Yes	Yes	No
	13	EQ5D	RCT	NDB	3%	Yes	Yes	Yes

Note: Shaded rows indicate base case options

Appendix 6: Sequential biologic sensitivity analyses

		MODEL OPTIONS					
		Health state utilities: EQ5D vs. SF6D	**Response at 6 months: RCTs vs. NDB**	**HAQ change after withdrawal: NDB vs. Scott**	**Discount rates**	**IXB dose increase**	**IXB round up to full vial**
ANALYSIS NUMBER	1	EQ5D	RCT	NDB	3%	Yes	Yes
	2	EQ5D	NDB	NDB	3%	Yes	Yes
	3	EQ5D	RCT	Scott	3%	Yes	Yes
	4	EQ5D	NDB	Scott	3%	Yes	Yes
	5	EQ5D	RCT	Scott	5%	Yes	Yes
	6	EQ5D	NDB	Scott	5%	Yes	Yes
	7	EQ5D	RCT	Scott	0%	Yes	Yes
	8	EQ5D	NDB	Scott	0%	Yes	Yes
	9	EQ5D	RCT	NDB	5%	No	Yes
	10	EQ5D	NDB	NDB	5%	No	Yes
	11	SF6D	RCT	NDB	3%	Yes	Yes

Note: Shaded rows indicate base case options