APPENDICES

Appendix A: Clinical questions and literature search

Question ID	Question wording	Study type filters used	Database and years
REFER1	In adults with a recent onset of an undifferentiated inflammatory arthritis, what features of the clinical presentation should a non specialist recognise in order to refer to specialist services, and how quickly should the referral be made in order to minimise the impact of disease on symptoms, joint damage, function and quality of life?	All study types	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
INVEST	In adults with a recent onset of an undifferentiated inflammatory arthritis, what are the investigative procedures that need to be performed to recognise the disease early and minimise the impact on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies, diagnostic studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
PROG	In adults with a recent onset of rheumatoid arthritis, and in established disease, what features of the clinical presentation help to identify the prognosis of the disease, and should those patients with poor prognosis be treated differently from the rest of the patient population in order to minimise the impact of disease on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies, prognostic studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
PATIENT	In adults with established rheumatoid arthritis, what is known of patient experiences of rheumatoid arthritis and its treatments, and how do patient perceptions and beliefs influence their preferences and outcomes with respect to symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies, qualitative studies incl. focus groups	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008 Psychinfo 1806–2008
EDU	In adults with recent onset of rheumatoid arthritis, and in established disease, what are the relative benefits of different patient information provision, and/or educational methods and/or different patient self management programs i) in relation to each other, ii) versus no specific information provision/ education with respect to symptoms, joint damage, function and quality of life?	All study types	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–008 Cinahl 1982–2008 Psychinfo 1806–2008
ANALG	In adults with a recent onset of rheumatoid arthritis, and in established disease, what are the benefits and harms of using analgesics on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008

continued

Question ID	Question wording	Study type filters used	Database and years
NSAID	In adults with a recent onset of rheumatoid arthritis, and in established disease, what are the benefits and harms of using non-steroidals and Cox-2 selective drugs on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
CORTICO	In adults with a recent onset of rheumatoid arthritis, and in established disease, what are the benefits and harms of using corticosteroids on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
DRUG1	In adults with a recent onset of rheumatoid arthritis, what sequence of single and combined disease-modifying and biological drugs will exert maximum impact on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
DRUG2	In adults with established rheumatoid arthritis, are there any circumstances under which disease-modifying drugs and biologics can be decreased and/or withdrawn without jeopardising the impact of disease on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
DRUG3	In adults with established rheumatoid arthritis, are biological drugs more effective than conventional disease-modifying drugs (singly, or in combination) in patients where there is ongoing disease activity with respect to symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
DMARD	In adults with a recent onset of rheumatoid arthritis, what are the benefits and harms of early introduction of disease-modifying drugs on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
ANAKINRA	In adults with established rheumatoid arthritis is anakinra an effective drug with respect to symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies, risk studies	Medline 2002–2008 Embase 2002–2008 Cochrane 2002–2008 Cinahl 2002–2008
MULTI	In adults with a recent onset of rheumatoid arthritis, what are the benefits and harms of multidisciplinary teams in order to minimise symptoms, joint damage, function and quality of life?	All study types	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
POD	In adults with a recent onset of rheumatoid arthritis, and in established disease, what aspects of podiatry can minimise the impact of disease on symptoms, joint damage, function and quality of life in the following groups?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008

continued

Question ID	Question wording	Study type filters used	Database and years
DIET	In adults with established rheumatoid arthritis, what aspects of diet have evidence that they influence symptoms, joint damage, function and quality of life positively?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008 AMED 1985–2008
PHYSIO	In adults with a recent onset of rheumatoid arthritis, and in established disease, what aspects of physiotherapy can minimise the impact of disease on symptoms, joint damage, function and quality of life in the following groups?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980 –2008 Cochrane 1800–2008 Cinahl 1982–2008
OCCU	In adults with a recent onset of rheumatoid arthritis, and in established disease, what aspects of occupational therapy can minimise the impact of disease on symptoms, joint damage, function and quality of life in the following groups?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
CAM	In adults with established rheumatoid arthritis, what aspects of complementary, alternative and other non-pharmacological interventions (acupuncture, copper bracelets, aromatherapy and massage) have evidence that they influence symptoms, joint damage, function and quality of life positively?	All study types	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008 AMED 1985–2008
MONIT	In adults with a recent onset of rheumatoid arthritis, and in established disease, what are the most effective methods to monitor the ongoing activity of the disease in order to minimise the impact of the disease on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
REVIEW	In adults with established rheumatoid arthritis, what should be the content of a regular review in terms of: • disease manifestations related to rheumatoid arthritis (eg extra-articular manifestations, cervical spine disease, secondary osteoarthritis, lymphoma, amyloidosis) • co-morbidities associated with rheumatoid arthritis (eg cardiovascular disease, osteoporosis, depression) and for each component, what should be the frequency of review in order to minimise the impact of disease on symptoms, joint damage, function and quality of life?	Systematic reviews, RCTs, observational studies, risk studies	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008
REFER2	In adults with established rheumatoid arthritis, what factors should determine the timing of referral for surgery in order to minimise the impact of disease on symptoms, joint damage, function and quality of life?	All study types	Medline 1950–2008 Embase 1980–2008 Cochrane 1800–2008 Cinahl 1982–2008

NOTE: The final cut-off date for all searches was 13 June 2008.

Appendix B: Scope of the guideline

This appendix contains (verbatim) the Scope document as signed off between NICE and the National Collaborating Centre for Chronic Conditions at the outset of the guideline development.

1 Guideline title

Rheumatoid arthritis: national clinical guideline for management and treatment in adults

1.1 Short title

Rheumatoid arthritis

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on the management and treatment of rheumatoid arthritis in adults for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix of scope). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.
b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.
c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Rheumatoid arthritis is a chronic, disabling autoimmune disease characterised by inflammation of the synovial tissue of the peripheral joints, which causes swelling, stiffness, pain and progressive joint destruction. For a small proportion of patients, inflammatory disease outside the joints (for example, eye and lung disease, vasculitis) can pose a significant problem.

b) Rheumatoid arthritis affects 1% of the population, or approximately 400,000 people in England and Wales. Of these, approximately 15% have severe disease. Rheumatoid arthritis is three times more prevalent in women than in men. The condition impacts severely on quality of life and is a considerable economic burden. It is estimated that 40% of people with rheumatoid arthritis will be unable to work within 5 years of diagnosis, and 50% within 10 years. The life expectancy of people with rheumatoid arthritis is reduced by 5–10 years compared with that of people without the condition, and 35–50% of this excess risk is accounted for by cardiovascular mortality.

c) A range of lifestyle, pharmacological, non-pharmacological, surgical and rehabilitation interventions can help to decrease inflammation, limit damage and improve function for people with rheumatoid arthritis, thereby maintaining or improving their quality of life.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix of the scope).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults with rheumatoid arthritis

4.1.2 Groups that will not be covered

a) Patients with other chronic inflammatory polyarthritis

4.2 Healthcare setting

a) Primary care, secondary care and intermediate care

4.3 Clinical management

a) Identification of the prognostic factors that indicate patients at greatest risk of persistent, damaging erosive and progressive disease

b) Pharmacological treatments for managing the condition including:
   - cyclo-oxygenase (Cox) II inhibitors
   - non-steroidal anti-inflammatory drugs (NSAIDs)

- corticosteroids
- disease modifying antirheumatic drugs (DMARDs)
- biological drugs

The guideline will attempt to identify the optimal sequencing of the effective pharmacological agents.

(Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.)

c) Non-pharmacological treatments relevant to rheumatoid arthritis, for example:
   - orthoses
   - podiatry
   - diet
   - physiotherapy
   - occupational therapy.

d) Pain management

e) Timing of referral for surgery

f) Support for patients and carers in managing rheumatoid arthritis, through education, self management and the provision of information and advice

g) Principal complementary and alternative interventions or approaches to care relevant to the guideline topic will be considered.

h) Where ineffective interventions and approaches to care are identified and where robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.4 Status

4.4.1 Scope

a) This is the consultation draft of the scope. The consultation period is 14 November to 13 December 2006.

b) The guideline will update the following NICE technology appraisal guidance, and will supersede the appraisals when it is published, with regard to rheumatoid arthritis.
   - Anakinra for rheumatoid arthritis. *NICE technology appraisal guidance 72* (2003). Available from: www.nice.org.uk/TA072
   - Osteoarthritis and rheumatoid arthritis – cox II inhibitors: *NICE technology appraisal guidance 27* (2001). Available from: www.nice.org.uk/TA027

c) Related NICE Technology Appraisals:
   - Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 36 (2002). Available from: www.nice.org.uk/TA036 (review in progress, which will include adalimumab; expected date of publication December 2007)

- Rituximab for the treatment of rheumatoid arthritis (publication date to be confirmed)
- Abatacept for the treatment of rheumatoid arthritis (publication date to be confirmed)
- Certolizumab pegol for rheumatoid arthritis (topic to be confirmed)

d) Related NICE clinical guidelines:
- Osteoarthritis: the care and management of adults with osteoarthritis (expected date of publication December 2007)

e) Related NICE interventional procedures:
- Artificial metacarpophalangeal and interphalangeal joint replacement for end-stage arthritis

4.4.2 Guideline

The development of the guideline recommendations will begin in June 2007.

5 Further information

Information on the guideline development process is provided in:
- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- The guidelines manual

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelines manual). Information on the progress of the guideline will also be available from the website.

Appendix C: Disease modifying antirheumatic drug combinations in early rheumatoid arthritis: a cost-effective analysis

C.1 Introduction

This cost-utility analysis evaluates the cost-effectiveness of combinations of disease modifying antirheumatic drugs in the treatment of patients with recent-onset rheumatoid arthritis. The model also evaluates the cost-effectiveness of using glucocorticoids alongside DMARD monotherapy in patients with recent-onset rheumatoid arthritis.

This report details the drug combinations investigated, the parameters included within the model, and the structure of the model. The results provided by the model are presented and discussed.

C.2 Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder affecting approximately 0.8% of the adult UK population.[5] Being a progressive disease and having a potentially early onset in a patient's lifetime leads to considerable societal and economic impact. Traditionally, patients have been treated using disease modifying antirheumatic drugs (DMARDs) along with anti-inflammatories, glucocorticoids, and analgesics. These treatments are relatively cheap, with drug costs representing about 13–15% of the total direct costs of treatment for RA.[401] However, newer, more effective, more expensive and more tolerable anti-TNF (biologic) drugs have been developed which may in time see the movement of more patients to more expensive treatments. As per current NICE guidance,[130] anti-TNF drugs are not available for patients until they have failed two traditional DMARDs (one being methotrexate), and so the use of DMARDs in recent-onset RA has a significant impact on both the future costs and future benefits accrued.

A large number of trials over the last 10–15 years have suggested an increased benefit in patients taking DMARDs in combination, instead of sequentially, with the aim of rapidly bringing a patient's disease under control. Traditional approaches to treating RA have focused on drug escalation, with DMARDs and steroids introduced sequentially and dosages titrated upwards. Whilst this traditional approach can see patients achieve disease-control, there is now much support to believe, both in clinical trials and clinical practice, that a 'slow' sequential monotherapy results in unsatisfactory long-term results as slow treatment and a failure to control a patients' disease from the outset can see poorer symptom control and irreversible damage to a patients joints.[231] Combinations of DMARDs and rapid changing of ineffective DMARDs will hope to bring a patient's disease under control much more quickly.

It is therefore important to evaluate the cost-effectiveness of these combinations of DMARDs as they will impact on the lifetime costs and benefits for the patient, especially as patients may fail to respond to two DMARDs more quickly than if they were taken sequentially and therefore move to more expensive biologic therapies earlier.

C.3 Methods

C.3.1 Comparator treatments

This analysis compares a range of combination DMARD therapies clinically evaluated in published studies against DMARD monotherapy, which is assumed to be standard clinical practice. The analysis also compares the use of glucocorticoids in combination with a DMARD, against DMARD monotherapy. The analysis will group the combinations by their general trend, and so the focus of the cost-effectiveness analysis will be comparing types of combination strategies, instead of modelling the numerous trials, many of which have similar protocols. This is based on the clinical opinion that there are no statistically significant differences in the efficacy of specific DMARDs. This allows for a full cost-effectiveness analysis with comparison to DMARD monotherapy as well as all alternative combination strategies.

C.3.1.1 Trials

A systematic review of the clinical and cost-effectiveness evidence was performed as part of the guideline development. The clinical searches were broadened to allow for evidence from non-UK populations and small studies. The defined aim of the review was to look for studies (see Table C.1) that '…investigated the efficacy and safety of early introduction of DMARDs with respect to symptoms, joint damage, function and quality of life in patients with a recent onset of RA.' Studies that were not a meta-analysis, randomised controlled trial, cohort study or case-control study, and also trials that did not report HAQ disease levels and ACR 20 or 50 response rates, were excluded.

Table C.1 Combination DMARD trials

Name	Arms	Reference
BEST[258]	Monotherapy Step Up Combination (Combo) Parallel Combo	Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
TICORA[242]	Routine Step Up Intensive Step Up	Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004; 364(9430):263–9.
TICORA2[402]	Intensive Step Up Triple Parallel Combo	Saunders SA, Capell HA, Stirling A et al. Triple Therapy in Early Active Rheumatoid Arthritis. A randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis & Rheumatism 2008; 58(5) May 1310–1317

continued

Table C.1 Combination DMARD trials – *continued*

Name	Arms	Reference
Dougados[403]	Sulphasalazine (SSZ) monotherapy Methotrexate (MTX) monotherapy Parallel Combo	Dougados M, Combe B, Cantagrel A et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52-week clinical trial of sulphasalazine and methotrexate compared with the single components. Annals of the Rheumatic Diseases 1999; 58; 220–225
Gerards[404]	Monotherapy Parallel Combo	Gerards AH, Landewe RBM, Prins APA et al. Cyclosporin A monotherapy versus cyclosporin A and methotrexate combination therapy in patients with early rheumatoid arthritis: a double blind randomised placebo controlled trial. Annals of the Rheumatic Diseases 2003; 62; 291–296
CIMESTRA[246]	Steroid + Monotherapy Parallel Combo	Hetland ML, Stengaard-Pedersen K, Junker P et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 2006; 54(5):1401–9.
Proudman[63]	Monotherapy Parallel Combo	Proudman SM, Conaghan PG, Richardson C et al. Treatment of poor-prognosis early rheumatoid arthritis. Arthritis & Rheumatism. 2000, 43(8) 1809–1819
Miranda[405]	Monotherapy Parallel Combo	Miranda JM, Alvarex-Nemegyei J, Saavedra MA et al. A Randomized, Double-Blind, Multicenter, Controlled Clinical Trial of Cyclosporine Plus Chloroquine vs Cyclosporine Plus Placebo in Early- Onset Rheumatoid Arthritis. Archives of Medical Research 35 (2004) 36–42
Sarzi-Puttini[406]	Monotherapy Parallel Combo (Hydroxychloroquine) Parallel Combo (MTX)	Sarzi-Puttini P, D'Ingianna E, Fumagalli M et al. An open, randomized comparison study of cyclosporine A, cyclosporine A + methotrexate and cyclosporine A + Hydroxychloroquine in the treatment of early severe rheumatoid arthritis. Rheumatology International (2005) 25; 15–22
Marchesoni[407]	Monotherapy Parallel Combo	Marchesoni A, Battafarano N, Arreghini M et al. Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. Rheumatology 2003; 42; 1545–1549
Van den Borne[408]	Monotherapy Parallel Combo (low dose) Parallel Combo (high dose)	Van den Borne BEEM, Landewe RBM, Goeithe HS et al. Combination Therapy in Recent Onset Rheumatoid Arthritis: A Randomized Double Blind Trial of the Addition of Low Dose Cyclosporine to Patients Treated with Low Dose Chloroquine. The Journal of Rheumatology, 1998, 25(8) 1493–1498

continued

Table C.1 Combination DMARD trials – *continued*

Name	Arms	Reference
FIN-RACo[250]	Steroid + Monotherapy Step Down Combo	Möttönen T, Hannonen P, Leirisalo-Repo M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999; 353:1568–73.
COBRA[253]	Monotherapy Step Down Combo	Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997; 350:309–18.

C.3.1.2 Treatment regimens

The range of treatment regimens, with different dosages, specific drugs and overall 'styles' for adding on or removing drugs from the regimen means that modelling each trial separately would be unnecessary in the context of the policy decisions being made. The majority of the trials are relatively small (N<100) and so it is unlikely that one trial will provide the weight to make a confident conclusion about a specific DMARD regimen. To provide a useful model without over-simplifying the complex nature and treatment of RA has been attempted by grouping together the trials into groups of similar treatment regimens. Many trials provide very similar strategies and so formally combining them in a meta-analysis will provide more weight to the conclusions (see Table C.2). The methods used to combine trials into strategies and how comparison is drawn between different groups is explained in detail later in the report under C.3.3.1 – Efficacy.

Table C.2 Combination strategy groups

Treatment Group	Explanation	Trial arms included
Control Arm	DMARD monotherapy (First line Methotrexate 15mg/week, Second line Sulphasalazine 1g/day)	Dougados – SSZ Dougados – MTX Capell Van den Borne BEST Gerards Proudman Miranda Sarzi-Puttini Marchesoni COBRA
Step Up Combination	One or more DMARDs are added (stepped-up) on top of a previous monotherapy regimen	BEST – Step Up Arm TICORA – Routine Arm

continued

Table C.2 Combination strategy groups – *continued*

Treatment Group	Explanation	Trial arms included
Parallel Combination	Two or more DMARDs are given in combination	Dougados BEST – Parallel Arm Gerards CIMESTRA Proudman Miranda Sarzi-Puttini CSA + HCQ Sarzi-Puttini CSA + MTX Marchesoni Van den Borne (two arms averaged) TICORA 2 – Triple Therapy
Step Down Combination	Initial parallel combination before specific DMARDs are removed	COBRA Fin-RACo
Intensive Step Up Combination	A parallel strategy where dosages of DMARDs are rapidly increased to above their recommended BNF dose	TICORA – Intensive Arm TICORA2 – Intensive Arm
Steroid + Monotherapy	Where glucocorticoids are used alongside a DMARD monotherapy regimen	Capell Fin-RACo Monotherapy Arm CIMESTRA

C.3.2 Model structure

The economic model is in the form of a Individual Patient Simulation – that is, it models the course of disease over time with changes to important variables at time-points where events (starting treatment, withdrawing from treatment, death) occur. The model generates a patient, whose characteristics (baseline age, HAQ, gender) are determined by UK rheumatoid arthritis survey evidence.[401] The model tracks individual patients one at a time through the treatment strategies. The time at which events occur and the results of those events is dependent on the patients past history and a range of characteristics specific to the individual.

Individual patients are followed from the time of starting a first-line DMARD strategy until death, with changes calculated every 6 months. Unlike cohort model approaches, where a population is tracked through a model, individuals are modelled one at a time. At every 6-month point the route taken by that individual patient is determined by a random number generator 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. The expected costs and benefits of each comparison are calculated, and this allows the assessment of the overall cost-effectiveness of each strategy in terms of cost per QALY. The model was developed in MS Excel.

C.3.2.1 Duration

The model has a lifetime duration, to allow all possible costs and benefits that are accrued to be captured by the model. With RA being a lifelong chronic condition, and evidence showing early

treatment having a lifelong impact on the future progression of the disease it is important that the model aggregates costs and benefits accrued in a patient's lifetime. For computational purposes, the lifetime duration is assumed to be fifty years from the disease onset, as the mean patient age is 54.8 years (SD = 13.6).[231]

In the model, HAQ and costs are calculated at 6-month time points (cycle-length). Initial response to a treatment is assumed to occur in the first time period (6 months). Depending on the age of the patient, the model 'runs' for the length of the patients lifetime to aggregate their expected costs and utility scores for each remaining cycle (calculated by life tables).

C.3.2.2 Clinical pathway

The model tracks patients over 6-monthly intervals from the initial decision to start a patient on a specific DMARD combination strategy or monotherapy, until the end of their lifetime. As the patients who enter the model are DMARD and biologic naïve, the model is actually tracking patients with RA through the whole of their medical treatment for RA. The model runs each hypothetical patient through all arms (all combinations and monotherapy). Figure C.1 is a decision algorithm which illustrates the model.

Patients who begin a new treatment are then simulated as to whether they are an ACR20, 50 or a non-responder. This initial response to treatment is mapped to the patient's HAQ profile, which is converted to a utility estimate. Patients who do not achieve an ACR20 or 50 response at 6 months progress to their next treatment (2nd DMARD monotherapy or biologics). Patients who do achieve an ACR20 or 50 response at 6 months are then simulated through a period on treatment, which is determined by the 6-month withdrawal rate of that strategy due to a loss of efficacy or an adverse event. Patients who are on treatment for longer than 6 months see a gradual worsening of their HAQ until they are withdrawn from treatment, at which time their HAQ rebounds by the same amount as the initial gain at 6 months. These fundamental assumptions are discussed in more detail later in the report, and investigated in the sensitivity analysis.

Once a patient has been withdrawn from either their 2nd monotherapy DMARD or their initial combination, they progress to biologic therapies, which are modelled as assigned lifetime costs and QALYs from an existing model of biologics. For further detail about how this is modelled, please see the section on 'Biologics' later in this report.

The level of a patient's disease in the model is measured in their Health Assessment Questionnaire (HAQ) score, for more details on how this, see the 'HAQ' subsection in 'Model Inputs'.

C.3.2.3 Limitations

Structurally, the model has a number of notable limitations. The first is that although the model is a patient-level simulation, the clinical data is based on clinical trials, not a registry and so patient covariates are not included to determine differences in clinical response or treatment withdrawal. Secondly the NICE guidance on biologic therapies specifies that patients only progress to biologics after failing two DMARDs (one being methotrexate and both tried for at least 6-months) and a patient having a Disease Activity Score (DAS) of more than 5.1. As the model is HAQ based, and there is no available conversion between HAQ and DAS, this requirement was left out of the model and it was assumed that patients who had failed two DMARDs would have active disease and be eligible for biologics.

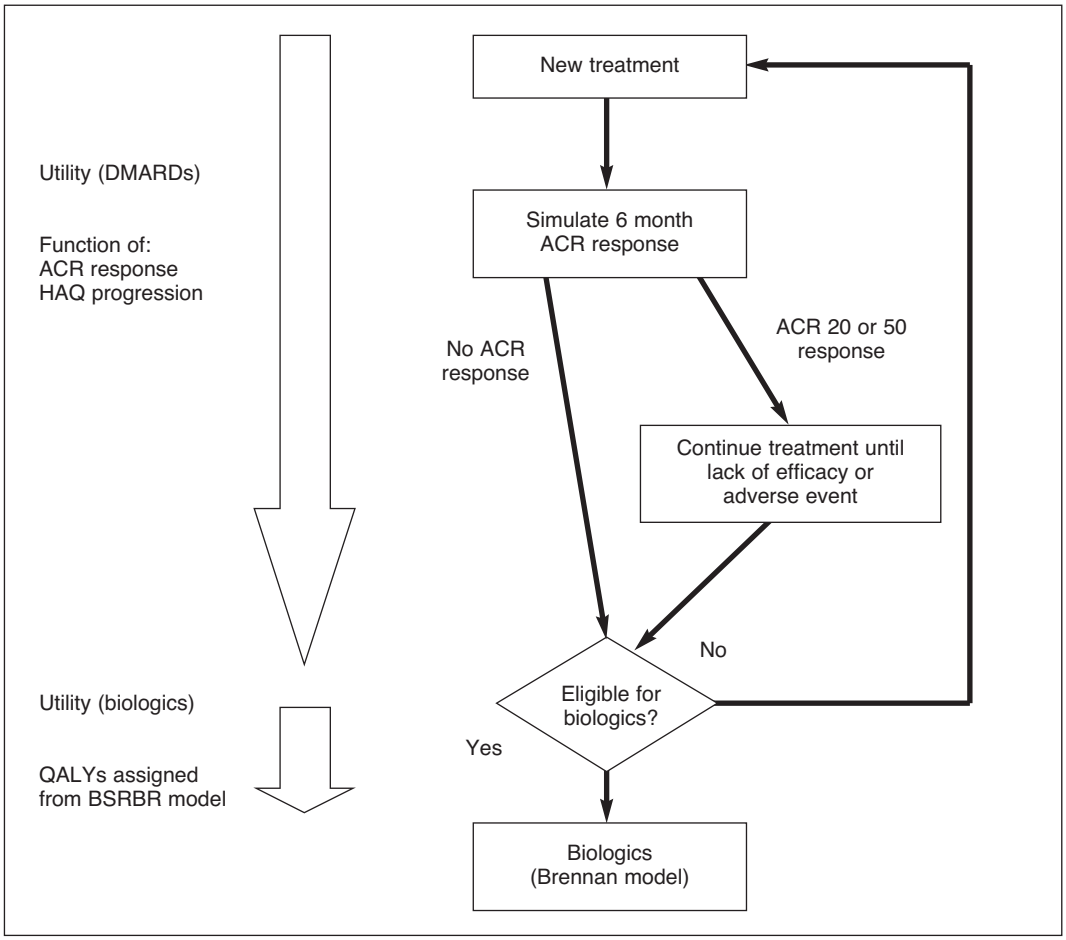

Figure C.1 Model diagram

C.3.3 Model inputs

C.3.3.1 Efficacy

Efficacy data from clinical trials, in the form of ACR20 and ACR 50 responses, are used in the cost effectiveness model for each of the alternative treatment strategies. Whilst individual trials make comparisons between two or more strategies, providing direct evidence of the relative treatment effect, no single trial exists that has made comparisons between all strategies of interest.

To account for this range of direct and indirect evidence, a mixed treatment comparison method was adopted[409,410] (also known as a network meta-analysis).[411] This method extends the approach of meta analysis but allows the different strategies to be compared to each other, including where no primary trials have made such a comparison, that is using indirect evidence. The approach maintains the randomised estimates from within each individual study. The crucial requirement to enable these methods to be applied is that the evidence is *connected* that is, for each treatment, there is a chain of pair-wise comparisons that connects it to every other treatment.

The studies included in the analysis were identified via systematic review with additional references identified by the Guideline Development Group. Where data were reported at 6 months from baseline this was used.

Random effects regression models were fitted. Only one multi arm study was identified and it was therefore not considered important to adapt the model to take the correlation induced by this single study into account. The analysis was based on the numbers of patients achieving ACR20 and ACR50 in the trials to obtain estimates of the log odds ratio of each treatment strategy relative to each other. In the cost effectiveness model, baseline probabilities of achieving ACR20 and ACR50 for patients treated with DMARD monotherapy were calculated separately as the weighted average from the relevant trial arms. The mixed treatment comparison estimates of the log odds ratios for each treatment strategy compared to monotherapy were used to estimate the probability of ACR20/50 response for the other strategies. The log odds ratios were characterised as independent normal distributions in the cost effectiveness model.

The analyses were conducted using Bayesian Markov Chain Monte Carlo Methods using WinBUGS.[412] The code for these analyses is from the University of Bristol.[413] We calculated the residual deviance and used this as a measure of the goodness of fit for the models. Under the null hypothesis that the model provides an adequate fit to the data, it is expected that residual deviance would have a mean equal to the number of unconstrained data points.[414,415] Plots to assess convergence and autocorrelation were examined and the effect of thinning the chains considered where appropriate. Analyses were also run with different starting values to check the effect on the model outputs.

In 9 studies (18 trial arms) data were only reported at 1 year after baseline and therefore these were used.

A total of thirteen trials comparing six treatment strategies were included in the analysis. Details of these studies are included in Table 3.

Table C.3 Summary of trial characteristics and ACR responses

Name	Arms	n	HAQ (mean (sd))	Disease duration (mean months)	6 months ACR20	6 months ACR50
BEST[258]	Monotherapy	126	1.4 (0.7)	5.8	0.48	–
	Step Up Combination	121	1.4 (0.6)	6.5	0.57	–
	(Combo)	133	1.4 (0.7)	6.0	0.71	–
	Parallel Combo					
TICORA[242]	Routine Step Up	55	1.9 (0.7)	20	0.64	–
	Intensive Step Up	55	2.0 (0.8)	19	0.91	–
TICORA2[402]	Intensive Step Up	47	2.0 (0.7)	13	0.77	0.60
	Triple Parallel Combo	49	1.9 (0.7)	10	0.76	0.51
Dougados[403]	Sulphasalazine (SSZ) monotherapy	68	1.38	12	0.59	
	Methotrexate (MTX) monotherapy	69	1.25	11.5	0.59	
	Parallel Combo	68	1.32	12	0.65	–

continued

Table C.3 Summary of trial characteristics and ACR responses – *continued*

Name	Arms	n	HAQ (mean (sd))	Disease duration (mean months)	6 months ACR20	6 months ACR50
Gerards[404]	Monotherapy	60	1.36 (0.63)	2.7	0.47	0.25
	Parallel Combo	60	1.43 (0.69)	2.9	0.56	0.48
CIMESTRA[246]	Steroid + Monotherapy	80	0.9	3.9	0.68	0.52
	Parallel Combo	80	1.0	3.2	0.85	0.65
Proudman[63]	Monotherapy	40	1.4 (0.6)	8.9	0.45	0.31
	Parallel Combo	42	1.4 (0.8)	8.4	0.58	0.40
Miranda[405]	Monotherapy	74	1.1 (0.6)	12.4	0.63	0.47
	Parallel Combo	75	1.1 (0.6)	13.0	0.64	0.48
Sarzi-Puttini[406]	Monotherapy	36	1.33 (0.57)	14.81	0.48	0.17
	Parallel Combo (Hydroxychloroquine)	35	1.42 (0.54)	17.63	0.54	0.2
	Parallel Combo (MTX)	34	1.44 (0.67)	15.15	0.77	0.59
Marchesoni[407]	Monotherapy	31	1.3 (0.7)	10.8	0.61	0.42
	Parallel Combo	30	1.3 (0.6)	10.8	0.53	0.50
Van den Borne[408]	Monotherapy	29	0.98 (0.47)	5.6	0.28	–
	Parallel Combo (low dose)	29	1.07 (0.62)	3.8	Averaged	
	Parallel Combo (high dose)	30	1.03 (0.42)	3.8	0.42	–
Fin-RACo[250]	Steroid + Monotherapy	98	0.9 (0.6)	8.6	–	0.60
	Step Down Combo	97	0.9 (0.6)	7.3	–	0.74
COBRA[253]	Monotherapy	79	1.4 (0.7)	4	0.49	0.27
	Step Down Combo	76	1.5 (0.7)	4	0.72	0.49

Not all the studies reported both ACR20 and 50. For one study[258] the authors were contacted directly for ACR50 response data since the published reports stated that this outcome was included in the trial but the results were not reported in the publication. Figure C.2 shows the network of evidence identified for the analysis for ACR20 and ACR50. It can be seen that each of the 6 treatment strategies are connected via the network of evidence. There are 15 pairwise comparisons between the 6 treatment strategies. Only one comparison, between monotherapy and parallel combination, had more than a single study providing direct evidence. Eight studies provided ACR20 data for this comparison and 6 reported ACR50 data. Table C.4 provides the log odds ratios and included trials for each of the treatment strategies.

Table C.4 Treatment strategies

Strategy	ACR20 log odds ratio	SD	ACR50 log odds ratio	SD	Trial	6-months or 1 year ACR
Monotherapy	–	–	–	–	Dougados – SSZ	1 year
					Dougados – MTX	1 year
					Capell	6 months
					Van den Borne	24 weeks
					BEST	6 month*
					Gerards	48 weeks
					Proudman	48 weeks
					Miranda	1 year
					Sarzi-Puttini	1 year
					Marchesoni	1 year
					COBRA	28 weeks
Step-up	0.010	0.232	–0.318	0.862	BEST – Step Up Arm	6 months
					TICORA – Routine Arm	1 year
Parallel	0.568	0.568	0.890	0.358	Dougados	1 year
					BEST – Parallel Arm	6 months
					Gerards	48 weeks
					CIMESTRA	6 months
					Proudman	48 weeks
					Miranda	1 year
					Sarzi-Puttini CSA + HCQ	1 year
					Sarzi-Puttini CSA + MTX	1 year
					Marchesoni	1 year
					Van den Borne (two arms averaged)	24 weeks
					TICORA 2 – Triple Therapy	1 year
Intensive	1.197	0.612	1.501	1.287	TICORA – Intensive Arm	1 year
					TICORA2 – Intensive Arm	1 year
Step-down	1.003	0.344	0.951	0.709	COBRA	28 weeks
					Fin-RACo	6 months
Steroid	0.136	0.248	0.280	0.749	Capell	All 6 months
					Fin-RACo Monotherapy Arm	
					CIMESTRA	

The baseline (DMARD monotherapy) probabilities of ACR20 / ACR50 response at 6 months was estimated as 0.502 and 0.315 respectively.

The models for ACR20 and ACR50 had residual deviances of 28.1 and 23.1 respectively which were close to the number of unconstrained data points (27 and 23 respectively), indicating a good model fit.

The estimated log odds ratios for the other treatment strategies are shown in Table C.5.

* Data provided through correspondence with author.

Table C.5 Log odds ratios (se) from mixed treatment comparison model for intensive DMARD strategies relative to DMARD monotherapy

Treatment strategy		LOR (CI)	
Parallel vs monotherapy	ACR20	1.72	(1.11 to 2.51)
	ACR50	2.50	(1.14 to 4.80)
Step up vs monotherapy	ACR20	1.55	(0.46 to 3.96)
	ACR50	1.39	(0.16 to 5.30)
Step down vs monotherapy	ACR20	3.25	(0.84 to 8.87)
	ACR50	3.34	(0.59 to 10.20)
Parallel intensive vs monotherapy	ACR20	13.02	(1.35 to 50.01)
	ACR50	25.57	(0.55 to 105.40)
Steroid vs monotherapy	ACR20	1.23	(0.47 to 2.53)
	ACR50	1.72	(0.27 to 5.68)
Step up vs parallel	ACR20	0.93	(0.26 to 2.53)
	ACR50	0.65	(0.06 to 2.58)
Step down vs parallel	ACR20	1.98	(0.48 to 5.73)
	ACR50	1.49	(0.24 to 4.75)
Parallel intensive vs parallel	ACR20	7.87	(0.80 to 31.23)
	ACR50	15.40	(0.22 to 48.71)
Steroid vs parallel	ACR20	0.73	(0.28 to 1.54)
	ACR50	0.72	(0.12 to 2.39)
Step down vs step up	ACR20	2.87	(0.40 to 9.92)
	ACR50	5.79	(0.27 to 26.65)
Parallel intensive vs step up	ACR20	8.28	(1.51 to 27.42)
	ACR50	13.14	(1.24 to 52.97)
Steroid vs step up	ACR20	1.07	(0.20 to 3.09)
	ACR50	3.14	(0.14 to 14.60)
Parallel intensive vs step down	ACR20	5.94	(0.36 to 26.85)
	ACR50	14.85	(0.15 to 63.79)
Steroid vs step down	ACR20	0.57	(0.09 to 1.76)
	ACR50	0.65	(0.12 to 2.13)
Steroid vs parallel intensive	ACR20	0.23	(0.02 to 0.95)
	ACR50	0.75	(0.01 to 3.40)

Note: figures in brackets are 95% credible intervals.

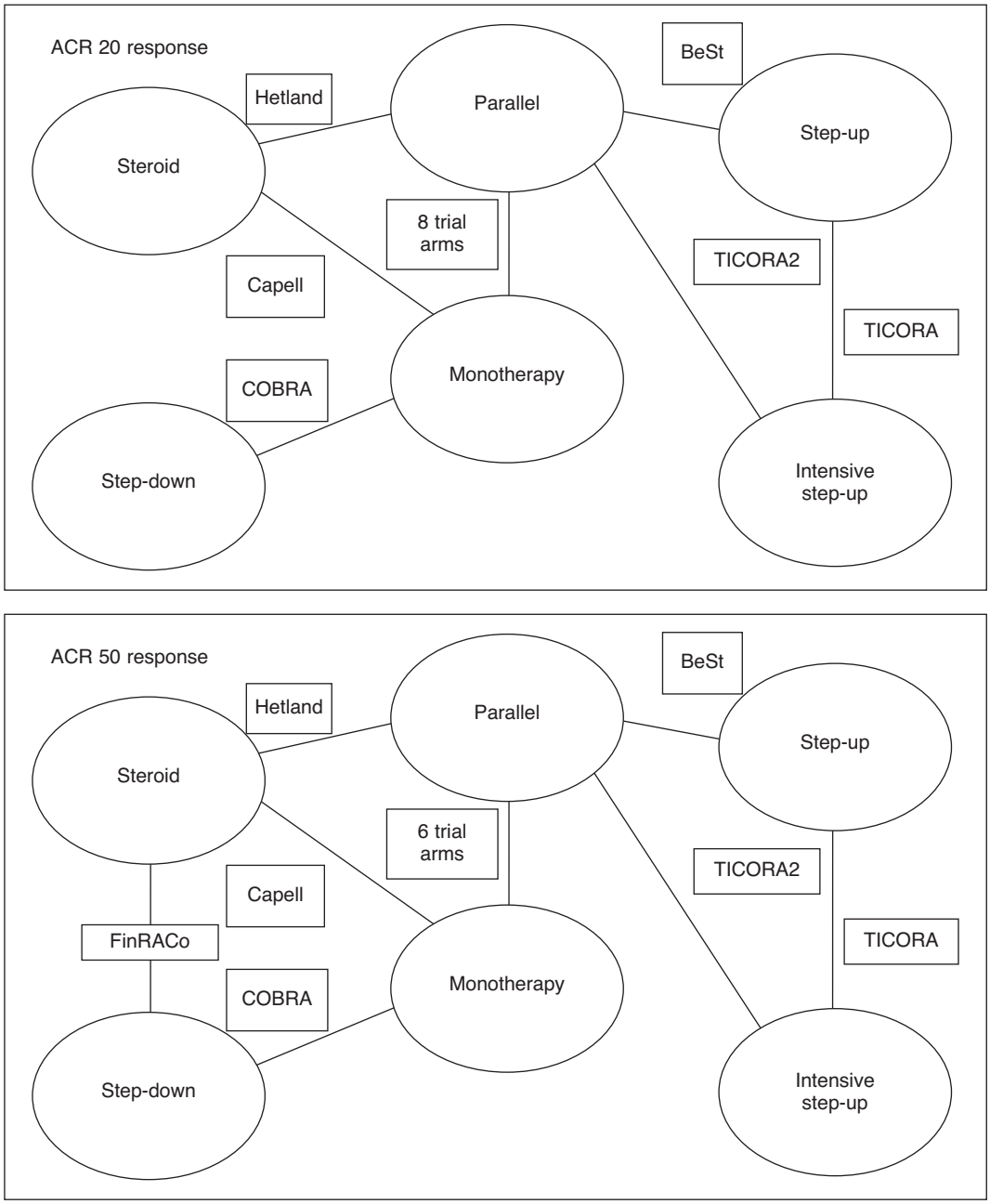

Figure C.2 Network of evidence for ACR20 (a) and ACR50 (b) response in recent onset rheumatoid arthritis by DMARD treatment strategy. Each treatment strategy is represented by a node in the network. Each line between the nodes represents a pair of arms from a trial and the number or name on the line indicates the number of pairs of trials arms or the name of the trial that made the comparison.

C.3.3.2 Withdrawal

The 6-month withdrawal rate was estimated (see Table C.6) for each treatment strategy by taking a weighted average of the patients withdrawn from each arm of the trials. 6-month withdrawals were specifically for a loss of efficacy or an adverse event. If 6-month rates were not given then the number of patients who were withdrawn annually was halved. In the model, the probability of withdrawing was held constant for each 6-month time period that a patient was

on a treatment. A random-number generator was used to simulate when a patient would withdraw from a treatment. Beta distributions were assigned to reflect the uncertainty from the sum of withdrawals and trial participants in each treatment strategy.

Table C.6 6-month withdrawal rates

Strategy	6-month withdrawal rate
Monotherapy	0.095
Step-up	0.020
Parallel	0.060
Intensive	0.049
Step-down	0.026
Steroid	0.074

For the monotherapy arm, both the probability of achieving an ACR 20 or 50 response, and the rate of withdrawal were assumed to be the same for both 1st DMARD and 2nd DMARD treatment before biologics.

C.3.3.3 Health Assessment Questionnaire

The most recorded measure of disease activity in the trials is the Health Assessment Questionnaire (HAQ), a measure of functional ability. HAQ is used as the measure of a patients level of disease severity in all recent cost-effectiveness analyses of RA. There is an established evidence base to the relationship between HAQ and Health Related Quality of Life (HRQoL),[416] and so a regression analysis and mapping algorithms have been used to convert HAQ to health utility values. These are investigated in the sensitivity analysis.

ACR response is the most commonly reported measure of response in the clinical trials and so has been incorporated into the model as an indication of the clinical impact at 6-months of a treatment strategy on a patient's level of disease activity.[417] The ACR response criteria defines a ACR 20 or ACR 50 response as a 20% or 50% reduction in their disease activity, (defined as a 20% or 50% reduction of their swollen joint count, plus an improvement in three of five other core measures). The 20% or 50% response cannot be seen as a 20% or 50% improvement in a patient's HAQ level, as they are fundamentally different measures of a patient's disease activity. Regression of a large longitudinal outcomes bank, the National Databank for Rheumatic Diseases (NDRD) was performed in a previous cost-effectiveness analysis and estimated a percentage HAQ improvement for an ACR 20 and ACR 50 response at 6-months to be 37.8% and 85.3% respectively.[418] Therefore in the model, when a patient is simulated as having an ACR 20 response at 6-months, their HAQ has improved by 37.8% from their baseline HAQ level.

Once a patient has had their ACR response simulated, their disease level (HAQ) increases at an annual rate of 0.0418, as estimated in a meta-analysis of long one natural disease data.[317] This data only looks at the annual progression of a patient's level of HAQ when on monotherapy

DMARDs, but for the baseline case is assumed across all treatment strategies. This assumption will be explored in the sensitivity analysis, with a differential rate applied to monotherapy and combinations.

When a patient withdraws from treatment, it is assumed that their HAQ rebounds back by the same amount that they may have gained from a 6-month ACR 20 or 50 response. So they will not rebound back to their original baseline HAQ level, as the time spent on treatment will assume that there is a gradual worsening of their disease level over time.

C.3.3.4 Outcomes

Quality Adjusted Life Years (QALYs) are the final outcome of the model, to allow for a full cost-effectiveness analysis of the alternative treatments. A QALY is calculated by a utility score for a patient's Health Related Quality of Life (HRQoL) multiplied by a year. The majority of the trials used to gain efficacy data for the DMARD combinations do not report any final HRQoL outcome measures, and so a reported intermediate disease-specific outcome measure has to be statistically 'mapped' to a utility estimate. Mapping is not an ideal solution, as disease-specific health outcomes do not fully capture the impact of treatments on a patient's Health Related Quality of Life (HRQoL). However mapping is a common approach adopted in the modelling of rheumatoid arthritis and this approach has been observed in all past RA technology appraisals.

The most recorded measure of disease activity in the trials is the Health Assessment Questionnaire (HAQ), and so is used to track the patient's level of disease activity through the model. HAQ may not capture all dimensions of HRQoL, especially pain. There is a risk that it may underestimate the impact of RA on patients, and the improvements that a treatment may provide. However in the Abatacept Single Technology Appraisal (STA), the Appraisal Committee notes that whilst it has limitations, 'it is the best means of estimating utility for the purpose of the economic analysis given the available data'.* HAQ correlates highly to utility measures such as the EQ5D, and so it is seen as appropriate to estimate a patients utility through mapping from HAQ. Mapping tools are available to derive utility from HAQ scores, for this model a regression analysis of US National Databank for Rheumatic Diseases (NDRD) is used. Utilities were mapped from HAQ-DI values of nearly 89,000 RA patients who were simultaneously administered the EuroQol (EQ-5D), HAQ, pain indices and SF-36 (see Table C.7). The HAQ scores were grouped into quarter-point categories from 0–3 and the associated model estimates for EQ-5D weighted health index are provided. The NDRD regression has applied the UK EQ-5D tariff.[419]

As well as the regression model, two linear transformations (Bansback et al. 2007[313] and Birmingham Rheumatoid Arthritis Model used for the Biologics Technology Appraisal)[420] were taken from the literature and used in the sensitivity analysis of the model. Table C.8 gives the details of the linear transformations. The basecase analysis uses the NDRD regression data as it is from a large sample of patients, and a common critique of linear transformations is they do not take a clear linear correlation.

* Section 4.3.10 www.nice.org.uk/page.aspx?o=388554

Table C.7 Wolfe NDRD utility regression

HAQ category	N	Mean utility (SD)	SE
0 – <0.25	13249	0.857 (0.16)	0.001
0.25 – <0.50	8305	0.803 (0.13)	0.001
0.50 – <0.75	8243	0.762 (0.14)	0.001
0.75 – <1.00	8717	0.713 (0.15)	0.002
1.00 – <1.25	9390	0.657 (0.15)	0.002
1.25 – <1.50	9596	0.590 (0.18)	0.002
1.50 – <1.75	9144	0.511 (0.19)	0.002
1.75 – <2.00	8113	0.427 (0.21)	0.002
2.00 – <2.25	5787	0.333 (0.24)	0.003
2.25 – <2.50	3110	0.229 (0.25)	0.002
2.50 – <2.75	1486	0.120 (0.27)	0.004
2.75 – <3.00	742	0.034 (0.33)	0.012

Table C.8 Linear HAQ to utility transformations

Reference	Conversion
Bansback	Utility = 0.76 – 0.28HAQ
BRAM/Hurst	Utility = 0.862 – 0.327HAQ

C.3.3.5 Adverse events

The implications of adverse drug events on costs or patient utility were not introduced directly into the model but were reflected indirectly in the treatment withdrawal rates.

C.3.3.6 Resource use

A HAQ to resource use estimation was used to estimate the long run extra usage of NHS resources, taken from the Resource Utilisation Norfolk Arthritis Register (NOAR).[417] Table C.9 shows the average resource use (hospital days, outpatient visits and % of joint replacements) grouped by patients HAQ level. These rates are combined with national costs to give an expected cost of additional direct resource use as a function of a patients HAQ level. The factoring of resource usage by HAQ level indirectly accounts for adverse events and associated complications due to having a high level of disease activity.

Table C.9 HAQ to resource use

HAQ	Hospital days (year)	Number of outpatient visits (year)	% patients who require joint replacement
0	0.2	0.6	0.3
0–1	0.5	1	0.8
1–2	1.2	1.5	2.3
2–3	5.1	2.1	4

Hospital days	£235.00*
Outpatient visit	£85.00[417]
Joint replacement	£7,410.32**

The estimated annual cost of resources used related to HAQ is £120.23, £261.78, £579.94 and £1673.41 for a patient with a HAQ of 0, 0–1, 1–2 and 2–3, respectively.

C.3.3.7 Unit costs

All unit costs are taken from literature and national unit costs (Table C.10). The cost of treatment for each trial was calculated, and the cheapest trial arm was used as the strategy cost in the model. This was because some trials used more expensive DMARDs, and the underlying assumption is that there is no significant difference in the efficacy of particular DMARDs and so the cheapest is to be used.

Table C.10 Costs (BNF 56 – September 2008)

Drug	Approx dose mg/day	Price £/pack	Pack size mg/tablet	Tablet/ packet	Cost drugs £/day	Drugs £/month
Sulfasalazine	2,000	£18.33	500	112	£0.65	£19.93
Methotrexate	1.15	£3.27	2.5	28	£0.05	£1.65
Hydroxychloroquine	300	£5.46	200	60	£0.14	£4.15
Prednisolone tablets	10	£0.60	5	28	£0.04	£1.30
Prednisolone injections mg/mL		£5.73	25	1		
Leflunomide	20	£51.13	20	30	£1.70	£51.88
Cyclosporine	175	£13.86	25	30	£3.23	£98.43
Betamethasone injections mg/mL		£1.22	4	1		
Folic Acid	0.7	£0.40	5	28	£0.01	£0.06
Outpatient Attendance (day case weighted average cost)		£85.00*				

*PSSRU – Unit Costs of Health and Social Care 2007.
** BMS abatacept submission, weighted average of all primary and revisional joint replacements, uprated from 2005/06 to 2006/07 using a 5.5% inflator (PSSRU – Unit Costs of Health and Social Care 2007).

In general each trial requires review and adjustment of the treatment at 3-monthly intervals. The intensive step-up strategy in the TICORA trial requires a second review after 3 months and from then it required monthly reviews for adjustment of the treatment and for administration of prednisolone injections, which is why the unit costs associated with the intensive step-up strategy are over three times higher than the second most costly treatment strategy. Costs included are drug costs, doctor/hospital consultation costs and drug administration costs. The 6-month total drug, administration and review costs are given in Table C.11.

Table C.11 6-month strategy costs

Strategy	6-month cost
Monotherapy	£251.40
Steroid	£269.98
Intensive step-up	£766.35
Step-down	£269.29
Step-up	£266.93
Parallel	£263.56

C.3.3.8 Population

The baseline characteristics (see Table C.12) of patients with recent-onset RA are taken from the Early Rheumatoid Arthritis Study (ERAS).[401] The study provides mean estimates and the standard deviation, from which the uncertainty is used to sample random patients in the model.

Table C.12 ERAS baseline patient characteristics

Parameter	Value	SD
Age (years)	54.8	13.6
Sex (proportion female)	66.6%	–
Disease duration (years)	0.68	0.508
HAQ at baseline	1.11	0.7

It is noted that there is likely to be a difference between the baseline characteristics of patients in the UK with RA, than those selected for the clinical trials used in this analysis. However it is assumed appropriate to base the analysis on UK patients as there is no clinical evidence suggesting a difference in the treatment effectiveness between patients with different baseline characteristics. The life expectancy of patients is determined from standard UK life tables.[421]

C.3.3.9 Biologics

Instead of recreating a lifetime model of the complete patient pathway of care for RA, the progression of patients to biologic therapies who have failed at least two DMARDs is modelled by 'bolting on' estimated costs and QALYs from an existing model. These values are taken from the patient level simulation model by Brennan et al.[317] The Brennan model provides registry-based evidence from the British Society for Rheumatology Biologics Register (BSRBR) that biologics are cost-effective in patients that have failed at least two DMARDS, with a baseline ICER of £23,882 per QALY.

The baseline lifetime cost for biologics is estimated as £57,919, and result in 5.1514 QALYs. Note that these values are discounted at the old NICE rate of 6% for costs and 1.5% for QALYs, and this is maintained for the biologic components of this model as these discount rates were used when NICE determined that biologics were cost-effective in patients that have failed at least two DMARDS. It is seen as appropriate to keep the biologic costs and QALYs discounted at the old rates to maintain biologics as a cost-effective strategy in this patient group, as is now current clinical practice in the NHS. Sub-group sensitivity analysis of the Brennan model indicates that updating the model to the new discount rates of 3.5% for costs and QALYs would return an ICER of £32,013. Also the Brennan model provides sub-group analysis across patient covariates such as age, HAQ level, disease duration and gender and so the model could potentially assign costs and QALYs that were proportionally adjusted by the sensitivity analysis reported. However as the sub-group analysis was only performed one-way on each of the covariates, it would be inappropriate to use them at all as the combined effect of a change across all covariates is not known. A limitation of using the Brennan model is that at the time of progression to biologics, on average the anti-TNF cohort had received 5 DMARDs, whilst the control cohort had received on average 3 DMARDs. Therefore the data provided by the BSRBR does not completely reflect our modelled assumption that patients progress to biologics after failure of two DMARDs.

C.3.3.10 Discounting

The estimated costs and QALYs were discounted at 3.5% per year, as per the NICE reference case.

C.3.3.11 Sensitivity analysis

Probabilistic Sensitivity Analysis (PSA) was performed. PSA quantifies uncertainty in the model by assigning distributions to parameters. Normal distributions were assigned to the patient baseline characteristics, the ACR response probabilities, log-odds ratios and for annual HAQ progression rates. Beta distributions were assigned to withdrawal rates. All other parameters were held constant. Sub-group sensitivity analysis was performed, along with one-way sensitivity analysis of a number of parameters and structural assumptions.

C.4 Results

C.4.1 Basecase analysis

The model results for 100 patients run through 1000 simulations of the patient level simulation are shown in Table C.13.

Table C.13 Model results – basecase analysis

Strategy	Cost	QALYs	Cost difference	QALY difference	ICER	Net Benefit	Net Benefit Rank
Monotherapy	£55,996	13.73				£218,604	3
Step Up	£50,791	11.91	–£5,205	–1.8	£2,852	£187,409	5
Parallel	£55,573	13.42	–£423	–0.3	£1,356	£212,827	4
Intensive	£61,046	15.77	£5,050	2.0	£2,482	£254,354	2
Step Down	£48,849	15.32	–£7,147	1.6	Cost Saving	£257,551	1
Steroid	£57,468	11.79	£1,472	–1.9	Dominated	£178,332	6

It is clear from the results that step-down combination is a dominating/cost-saving strategy, with an expected 1.6 QALYs gained whilst saving £7,147, when compared to monotherapy. The results also show that steroids plus DMARD monotherapy is a dominated strategy, which is more costly and less effective than DMARD monotherapy. Whilst the steroid strategy had a slightly better chance of achieving an ACR response, the small difference was countered by patients in monotherapy having to go through the strategy twice before moving to biologics, and therefore having another chance of seeing an ACR response and the associated gains in QALYs before moving to biologics.

The remaining strategies; step up, intensive step up and parallel combination all had estimated ICERs of under £3,000 per QALY. NICE recommends that advisory bodies should apply a cost-effectiveness threshold of between £20,000 and £30,000 per QALY* and so in this case step up, intensive step up and parallel combination are cost-effective strategies when compared to DMARD monotherapy. Figure C.3 (overleaf) provides a plot of the estimated cost and QALYs accrued for each of the comparator treatments.

The model was also run deterministically, using the point estimates for parameters. The results of a deterministic run of 100 patients through the basecase model are given in Table C.14. The results indicate that through a run of 100 patients, the results are generally similar to those when run probabilistically, although intensive step-up strategy becomes cost saving, due to the costs of this treatment being less than the monotherapy arm whilst maintaining a similar gain in QALYs. In terms of ACR20 and 50 response at 6 months, intensive step-up is a highly effective strategy, and this is attributable to gains in QALY and reductions in HAQ that are likely to see the significantly lower resource costs erase the difference in treatment costs. 6-months on monotherapy with HAQ>2 costs £1088.11, whilst 6-months on monotherapy with HAQ<1 costs £897.27.

* Social value judgements: principles for the development of NICE guidance www.nice.org.uk/media/873/2F/SocialValueJudgementsDec05.pdf

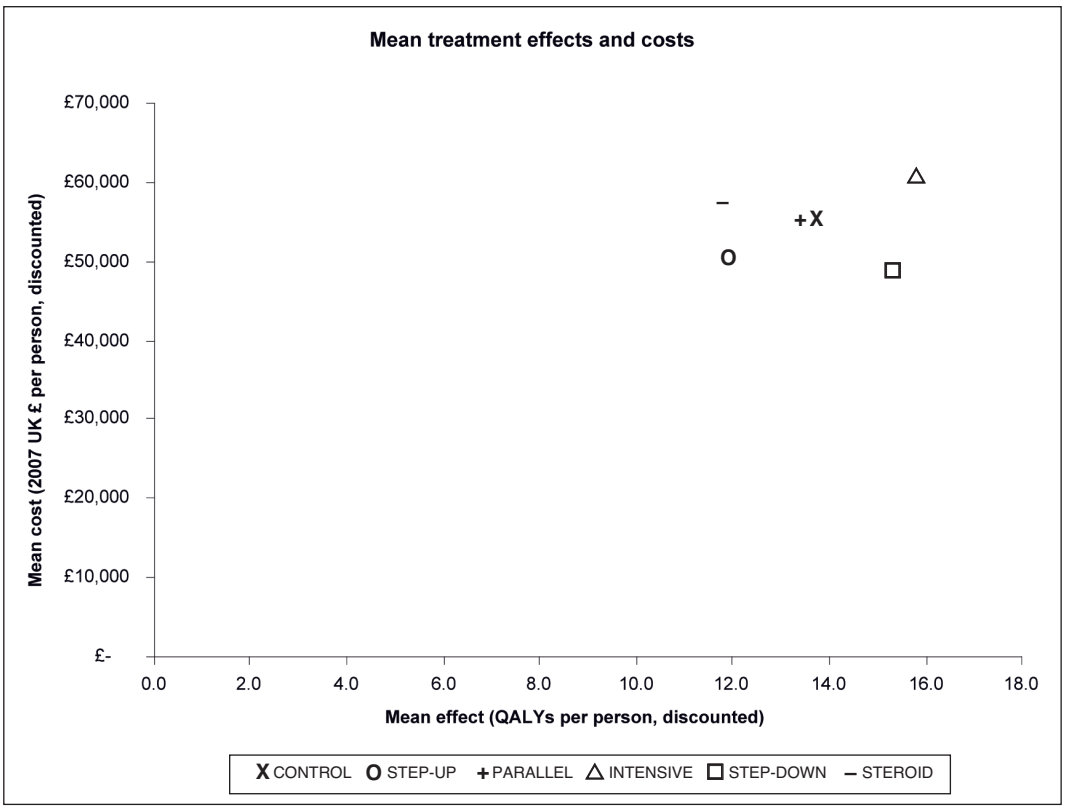

Figure C.3 Mean treatment costs and benefits – basecase analysis

Table C.14 Basecase analysis – deterministic results

Strategy	Cost	QALYs	Cost difference	QALY difference	ICER
Monotherapy	£57,106	14.41			
Step Up	£48,258	11.73	–£8,848	–2.67	£3,308
Parallel	£56,822	13.11	–£284	–1.29	£219
Intensive	£54,570	15.92	–£2,536	1.51	Cost Saving
Step Down	£51,986	16.57	–£5,120	2.16	Cost Saving
Steroid	£60,502	11.67	£3,396	–2.74	Dominated

Performing a mixed treatment comparison allows full incremental cost-effectiveness analysis between each of the comparators. The results of the full incremental analysis are given in Table C.15.

Table C.15 Incremental basecase analysis

Strategy	Cost	QALY	Net benefit	ICER	Comparator
Step Down	£48,849	15.3	£410,863	Cost-saving	Monotherapy
Intensive	£61,046	15.8	£412,025	£27,392	Step-down

(Note: Comparisons are against the next best, non-dominated treatment strategy)

Compared with the cheapest strategy, step down combination, all strategies are dominated by the laws of simple domination apart from intensive step-up. This means that the remaining strategies are more expensive and less effective, including DMARD monotherapy. When compared to step down combination, intensive step up has an incremental cost-effectiveness ratio of £27,392 per QALY.

C.4.1.1 Uncertainty

Probabilistic sensitivity analysis (PSA) was performed to reflect the uncertainty in the input parameters of the model and determine what this means for the results of the model. The results of the PSA are showing in Figure C.5. The cost-effectiveness acceptability curves (CEACs) show the estimated probability that a treatment option is cost-effective given the amount that we are willing to pay for a QALY (the cost-effectiveness threshold shown on the horizontal axis). This helps to reinforce the conclusion that at a NICE cost-effectiveness threshold of around £20,000 to £30,000 per QALY, step-down combination is the most likely cost-effective strategy when compared to monotherapy, with a probability of over 80%.

The CEAC also illustrates that there is considerable uncertainty around the relatively ranking of the other combination strategies. Figure C.6 is an incremental CEAC, which estimates which treatment is likely to be the most cost-effective when compared to all other comparators. It shows that at a threshold of £20,000 per QALY, step-down combination is the most likely to be the most cost-effective.

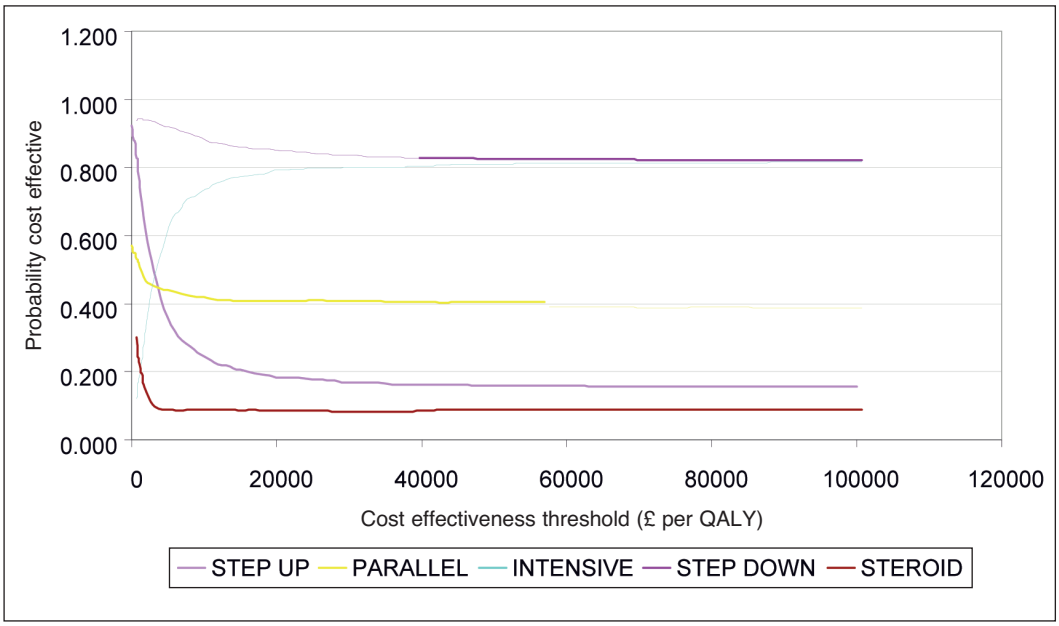

Figure C.4 Baseline analysis – CEAC common baseline

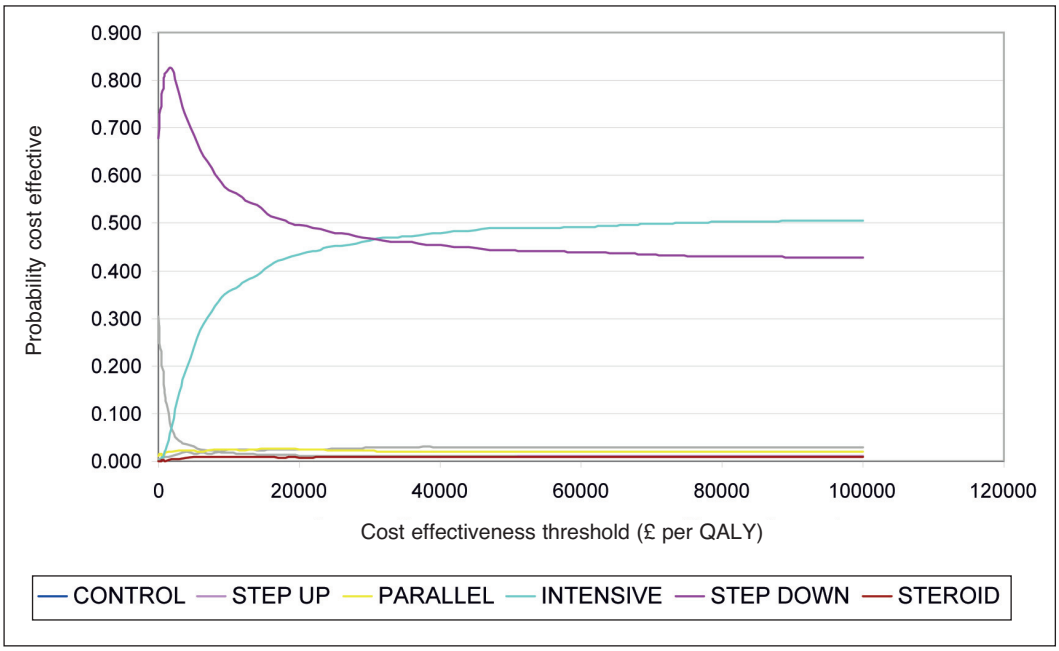

Figure C.5 Baseline analysis – incremental CEAC

C.5 Discussion

The basecase analysis in the previous section provides convincing evidence that a step-down combination strategy is an effective and cost-effective first line strategy for patients with RA. However this conclusion is based on a number of clinical assumptions which are tested through sensitivity analysis.

C.5.1 Treatment withdrawal

A key assumption of the model is that patients who do not achieve an ACR 20 or 50 response after 6-months will either move to biologics or begin a 2nd line DMARD monotherapy. This may be clinically inappropriate with a 6-month ACR response not fully capturing patients who may have yet to respond to their treatment, as well as capturing those who may have achieved a sub-ACR20 response but still achieved some form of disease control. Therefore the model was run with none responders continuing on their treatment until they are withdrawn due to a loss of efficacy or an adverse event. The model was run probabilistically, with 100 patients sent through 1000 samples and the results are given below in Table C.16.

Table C.16 Results – no switch for non-responders

Strategy	Cost	QALYs	Cost difference	QALY difference	ICER	Net Benefit	Net Benefit Rank
Monotherapy	£ 53,569	14.58	–	–	–	£221,031	3
Step Up	£ 45,578	15.37	–£7,991	0.8	Cost Saving	£192,622	5
Parallel	£ 54,975	16.19	£1,405	1.6	£872	£213,425	4
Intensive	£ 62,245	17.25	£8,676	2.7	£3,244	£253,155	2
Step Down	£ 46,718	17.25	–£6,851	2.7	Cost Saving	£259,682	1
Steroid	£ 57,457	15.06	£3,888	0.5	£8,096	£178,343	6

Interestingly, both step-up and step-down combinations are now a dominant strategy. This is because, referring back to Table C.6, these strategies have very low rates of withdrawals compared to the other strategies. Spending a much longer time on DMARD therapy gives a patient a long time for QALYs to accrue before withdrawing and then being assigned costs and QALYs for biologics, assuming they have not died before the end of their treatment.

Table C.17 compares the estimated length on treatment between the basecase analysis and a scenario when non-responders do not switch after 6 months.

Table C.17 Time on DMARDs analysis

	Non-responders switch				Non-responders do not switch			
	Cost	QALY	ICER	Time on DMARDs	Cost	QALY	ICER	Time on DMARDs
Monotherapy	£57,106	14.41		12.29	£ 53,569	14.58		17.97
Step Up	£48,258	11.73	£3,308	18.66	£ 45,578	15.37	Cost Saving	28.94
Parallel	£56,822	13.11	£219	12.13	£ 54,975	16.19	£872	17.13
Intensive	£54,570	15.92	Cost Saving	14.77	£ 62,245	17.25	£3,244	27.86
Step Down	£51,986	16.57	Cost Saving	23.78	£ 46,718	17.25	Cost Saving	23.18
Steroid	£60,502	11.67	Dominated	8.73	£ 57,457	15.06	£8,096	9.38

(Time on DMARDs is in half-years)

A conclusion from this is that there is clinical benefit in finding a DMARD that is effective for a patient. The standard clinical belief is that patients that are on drawn out monotherapy treatment will be on DMARDs much longer than combinations before they switch to biologics. However the evidence from the trials is that monotherapy has the greatest rate of withdrawals for loss of efficacy or for an adverse event. This could be because of the lower rate of clinical response seeing withdrawals, or just random variation due to the generally small nature of the trials. Either way it supports the clinical evidence suggesting that combination DMARDs are no more toxic or less safe than monotherapy DMARDs, and that there is no greater risk of adverse events (see Clinical Evidence for DMARDs in The Guideline document).

C.5.2 HAQ progression

The second key assumption of the model is that all patients on treatment will see an increase in their HAQ by a given annual rate.[317] However this data is based on DMARD monotherapy evidence, and as yet there has not been a long-run formal analysis of the progression RA in patients on combinations DMARDs. The follow-up evidence in BeSt and COBRA suggest that there is not a significant annual increase in their HAQ from 6-months until the end of follow-up. For this reason, the model was re-run with the HAQ annual progression assigned to the monotherapy group (see Table C.18), whilst the combination DMARD group saw no annual progression when they had an ACR20 or 50 response. As per the basecase analysis, non-ACR responders were switched to their relevant second line therapy.

The model was run probabilistically with 100 patients through 1000 simulations.

Table C.18 Probabilistic analysis – HAQ progression

Strategy	Cost	QALY	ICER
Monotherapy	£56,545	13.01	£–
Step Up	£51,061	11.74	£4,318
Parallel	£55,612	13.35	Cost Saving
Intensive	£61,160	15.67	£1,732
Step Down	£48,935	15.08	Cost Saving
Steroid	£57,546	11.75	Dominated

As expected, the results see a general improvement in the cost-effectiveness of the combination strategies when compared to monotherapy. Steroid plus monotherapy is still a dominated strategy, as the relatively fast withdrawal does not allow much benefit to accrue over time on treatment when compared to monotherapy. Parallel combination is now a dominating strategy, along with step down, whilst step up and intensive are highly cost-effective when compared to monotherapy. Until longer follow-ups and dedicated analysis on the HAQ progression of patients on combinations are available, the issue of how to model the long-term benefits of DMARDs will still exist.

C.5.3 Subgroup analysis

Deterministic subgroup analysis was performed to investigate whether baseline HAQ or patient age would have any strong influence on the outcomes and cost-effectiveness of each strategy. Tables C.19–C.21 give the results for the analysis when patients are split between baseline HAQ 0–1, 1–2, and 2–3. The results show that for steroid strategy, it is a dominated option for patients with a HAQ less than 1 but is cost-effective for patients with active disease. The remaining strategies are cost-effective (<£20,000 per QALY) or cost-saving across all baseline HAQ groups.

Table C.19 Deterministic subgroup analysis – HAQ<1

Strategy	Cost	QALY	ICER
Monotherapy	£58,064	13.73	£–
Step Up	£48,169	12.34	£7,140
Parallel	£54,683	12.87	£3,957
Intensive	£66,772	16.03	£3,781
Step Down	£48,008	15.36	Cost Saving
Steroid	£59,200	9.66	Dominated

Table C.20 Deterministic subgroup analysis – HAQ 1–2

Strategy	Cost	QALY	ICER
Monotherapy	£57,880	12.49	£–
Step Up	£44,544	13.76	Cost Saving
Parallel	£56,459	12.11	£3,742
Intensive	£62,996	15.24	£1,857
Step Down	£47,159	16.28	Cost Saving
Steroid	£59,638	13.18	£2,556

Table C.21 Deterministic subgroup analysis – HAQ 2–3

Strategy	Cost	QALY	ICER
Monotherapy	£57,643	12.73	£–
Step Up	£49,072	13.16	Cost Saving
Parallel	£55,385	14.20	Cost Saving
Intensive	£63,387	16.69	£1,448
Step Down	£46,746	15.83	Cost Saving
Steroid	£57,552	9.03	£25

Tables C.22 and C.23 show how the cost-effectiveness of each strategy varies depending on the age of the patient as they enter the model. Understandably the patients aged over 79 generally accrue less QALYs. Interestingly the parallel strategy is dominated in the younger group, whilst being a very cost-effective strategy in the older group. Because the clinical effectiveness is assumed not to vary by age, this wide difference is due to the wide uncertainty in the model and provides clear evidence that drawing conclusions from point estimates, and having no grasp of the uncertainty in the model, is inappropriate.

Table C.22 Deterministic subgroup analysis – age <50

Strategy	Cost	QALY	ICER
Monotherapy	£53,621	12.81	£–
Step Up	£53,556	12.15	£98
Parallel	£55,659	12.40	Dominated
Intensive	£63,603	16.26	£2,890
Step Down	£49,267	15.81	Cost saving
Steroid	£59,023	11.85	Dominated

Table C.23 Deterministic subgroup analysis – age >79

Strategy	Cost	QALY	ICER
Monotherapy	£56,048	13.76	£–
Step Up	£47,646	11.64	£3,970
Parallel	£53,596	13.18	£4,218
Intensive	£64,273	15.87	£3,899
Step Down	£45,294	14.96	Cost saving
Steroid	£58,821	10.78	Dominated

C.5.4 HAQ to utility

Whilst the basecase analysis uses the Wolfe NDRD analysis to convert HAQ to utility, there are two published linear conversions that transform HAQ into a utility score. The model was run deterministically through both of these transformation tools.

Table C.24 Deterministic – Bansback utility

Strategy	Cost	QALY	ICER
Monotherapy	£58,017	10.79	£–
Step Up	£52,075	9.81	£6,051
Parallel	£57,671	10.93	Cost saving
Intensive	£65,428	12.39	£4,637
Step Down	£48,339	11.58	Cost saving
Steroid	£59,512	8.79	Dominated

Table C.25 Deterministic – Hurst/BRAM utility

Strategy	Cost	QALY	ICER
Monotherapy	£55,077	10.44	£–
Step Up	£53,706	10.08	£3,898
Parallel	£57,886	10.79	£7,920
Intensive	£64,129	13.68	£2,790
Step Down	£49,578	12.01	Cost saving
Steroid	£56,926	10.67	£7,727

Both Tables C.24 and C.25 show that the resulting QALYs estimated are lower than the basecase analysis. However the difference in the costs would not have been caused by the uncertainty in the estimates and again show that drawing firm conclusions from a deterministic run of 100 patients is inappropriate.

C.5.5 Cost

The TICORA trial, that populated the intensive step-up strategy, included a cost-effectiveness analysis[242] which found the intensive arm to be more effective at no additional cost. There were higher inpatient costs in the standard step up arm which dominated the higher prescribing costs in the intensive arm. Because the costs of the strategies were estimated using the prescribing, administration and review costs of each of the strategies and direct extra admissions or admissions due to adverse events not being directly estimated, the modelled cost of intensive step up was higher than the standard step up strategy. The difference in cost was met by an appropriate gain in QALYs which sees intensive step-up as a very cost effective strategy. However it is important to elaborate on the reasons why the resulting conclusions are different from the original trial analysis.

It is also important to make reference to the estimation of costs of the strategies. The cost of each trial strategy was estimated, and then the cheapest strategy was taken for each of the groups. The dosages were generally similar, and so the fundamental assumption is that with no significant difference between the safety, efficacy and tolerability of the DMARDs, the cheapest drug(s) should be chosen to construct a DMARD combination. Apart from the intensive step-up strategy which required monthly monitoring and drug administration, the other strategies all had very similar costs, due to the relatively low costs of the drugs, and the key component being the number of admissions required.

Finally, in the context of actual clinical practise, it may not be appropriate that at the beginning of therapies that patients require only 3-monthly monitoring (see Table C.26). The model was re-run so that across all strategies monthly outpatient attendances were required and this extra cost was factored in. If a patient responded then that patient would then return to a rate of attendance as determined in the trial (All 3-monthly except for TICORA intensive step-up which required monthly attendances). The model was re-run probabilistically, with these extra monitoring costs, through 100 patients and 1000 simulations.

Table C.26 Monthly monitoring for first 6 months

Strategy	Cost	QALY	ICER
Monotherapy	£56,865	13.05	£–
Step Up	£51,941	10.89	£2,276
Parallel	£56,657	12.60	£458
Intensive	£62,199	14.55	£3,556
Step Down	£50,026	13.99	Cost Saving
Steroid	£58,142	11.26	Dominated

When compared to the basecase analysis, the results of the extra monitoring for the first 6 months are no difference in terms of the cost-effectiveness of any of the strategies, but there is a small increase in the cost of all strategies. It is important that any model accurately reflects clinical practice and so these results assume that extra monitoring is required, both for the risk of adverse events, and also to formally assess the level of function and disease to establish whether there has been a response to treatment.

C.5.6 Discount Rate

The model uses cost-effectiveness results from the Brennan et al. biologics model.[317] This model uses discount rates of 6% for costs and 1.5% for QALYs, as recommended by the old NICE Methods Guide. Since NICE provided guidance for biologics, they have revised their recommended discount rates to 3.5% for both costs and QALYs. This model currently uses the baseline output from the Brennan model to bolt on the biologics model. However the Brennan model also provides results if the new discount rates were used. This results in a change in anti-TNF cost from £57,919 to £72,398, a change in DMARD cost from £20,706 to £31,266, a decrease in anti-TNF QALYs from 5.15 to 4.27, and a decrease in DMARD QALYs from 3.59 to 2.98. These revised values were run in a deterministic sensitivity analyses. The results are given in Table C.27.

Table C.27 Using new discount rates for biologic progression

Strategy	Cost	QALY	ICER
Monotherapy	£69,169	15.27	£–
Step Up	£61,892	13.26	£3,624
Parallel	£68,773	14.40	£454
Intensive	£75,271	16.73	£4,179
Step Down	£59,929	16.72	Cost Saving
Steroid	£72,100	12.97	Dominated

As the results show, there has been no significant change to the cost-effectiveness of any of the strategies.

C.6 Conclusions

This cost-effectiveness analysis has provided conclusions on the use of combination DMARD strategies compared to DMARD monotherapy. The analysis has also provided conclusions on the use of steroids alongside DMARD monotherapy when compared to monotherapy alone. The analysis was focused on patients with rheumatoid arthritis who were both DMARD and biologic naïve.

The analysis took a lifetime perspective, which required the estimation of costs and QALYs for patients who had failed two DMARDs and were eligible for biologic therapies, and the subsequent costs and QALYs associated with biologic therapy. The analysis was based on two clinical assumptions, firstly that patients who did not achieve an ACR 20 or 50 response after 6 months moved to 2nd DMARD or biologics. Secondly, if a patient achieved an ACR 20 or 50 response then their HAQ worsened at a given rate. The ACR 20 or 50 response evidence is taken from thirteen randomised controlled clinical trials and mixed treatment comparison techniques are applied to allow the trials to be compared to each other. The specific protocols used in the trials are used to estimate the cost of each strategy, and the withdrawal rates for a loss of efficacy or an adverse event are taken from a weighted average of 6-month withdrawals from the trials.

A clear result from the basecase analysis is that it is cost-effective to provide a combination strategy of DMARDs as first line treatment for RA. The analysis shows that a step-down combination of DMARDs is likely to be a cost-saving strategy, and more than likely to be the most cost-effective strategy given a NICE threshold of between £20,000 and £30,000 per QALY. Incidentally, one of the two trials that provided the evidence for a step-down combination strategy, COBRA[253] provided a cost-effectiveness analysis in a Dutch setting and reported step-down combination to be a cost-saving strategy. In the COBRA trial, step-down therapy was performed using initial prednisolone, methotrexate and sulphasalazine with prednisolone and methotrexate tapered and stopped from week 28 to week 40. In the FIN-RACo trial,[250] patients were also given prednisolone, methotrexate and hydroxychloroquine which was increased if there was a poor response, and if not the dosages were tapered and stopped from between 9 to 18 months.

The basecase analysis determined that a strategy of monotherapy plus glucocorticoids is dominated (more costly and less effective) by DMARD monotherapy. This is due to the cost-differential not being covered by a significant increase in ACR response rate. However it is important to note that intensive step up, step up and step down all include glucocorticoids in the regimen and so steroids contribute to the effectiveness of a DMARD combination strategy.

However it is important to note the uncertainties over the rates of withdrawals and the probability of an ACR response. However PSA provides confirmation that at a threshold of £20,000 per QALY, step-down has an 86% likelihood of being cost-effective, whilst intensive step-up has an 80% likelihood, and parallel combination having a 40% likelihood. Incremental PSA analysis suggests that at a £20,000 per QALY threshold, step down is more likely to be the most cost-effective strategy than intensive step up.

Sub-group analysis was performed, modelling groups of patients according to their age and their baseline HAQ. The analysis emphasised the dangers of drawing conclusions of running a model deterministically, as there is great uncertainty in the model that cannot be accounted for when run using point estimates. The combinations therapies all maintained being cost-effective strategies when compared to baseline. The glucocorticoid alongside monotherapy group was found to become a cost-effective strategy when the model was run in patients with a baseline HAQ level above 1. Sensitivity analysis was performed on the conversion of HAQ to utility scores. The model was run through two linear transformations, both of which did not cause any DMARD combinations to become not cost-effective, and again highlight the uncertainty in the parameters.

A key assumption in the model is that all patients that respond to treatment will see an annual increase in their HAQ level. However, the evidence for this assumption is limited to DMARD monotherapy, and so sensitivity analysis was performed to determine the cost-effectiveness of combinations of DMARDs when they see a constant annual level of HAQ, and whilst monotherapy remains at the annual rate of increase. The re-run of the model concluded that parallel combination becomes a cost-saving strategy, steroid plus monotherapy remains dominated, and the other combinations all become more cost-effective, when compared to monotherapy. The sensitivity analysis has provided intuitive changes in the results, providing reassurance on the overall validity of the model.

This analysis has determined that step-down combinations of DMARDs are likely to be very cost-effective or even cost-saving, and other DMARD combinations are very likely to be cost-effective. However it has also highlighted the high level of uncertainty over the clinical evidence used to populate the model, as well as the structural/clinical decisions used to determine how patients withdraw from treatment, and how their disease level behaves whilst on treatment.

Further research could be done to assess the underlying reasons for patients withdrawing from treatment, which is a key driver for the results of this model. Further research is required to assess the long-term disease activity of patients on monotherapy DMARDs and combination DMARDs, as this has a substantial impact on the QALYs that a patient accrues whilst on treatment. Also the model could be expanded to fully incorporate biologic therapies into the analysis, providing a complete model of drug therapy for patients with RA. This could be done to either completely model the cost-effectiveness of all RA treatment strategies, or to assess the cost-effectiveness of biologic therapies against more effective DMARD combinations, as opposed to the common approach comparing the cost-effectiveness of biologics against monotherapy DMARDs.

Appendix D: Declaration of interests (GDG members)

Group member	Personal pecuniary interest	Personal family interest	Non-personal pecuniary interest	Personal non-pecuniary interest
Raashid Luqmani	Consultancy for Euro Nippon Kayaku on evaluating role of gusperimus – now terminated – in Wegener's granulamatosis	None	Abbott and Schering-Plough have provided financial support to the MSc course in Oxford, WHKH and RUN	None
Louise Warburton	None		None	I am a member of the Primary Care Rheumatology Society and on the editorial board of Rheumatology in Practice. I have inflammatory arthritis and am on anti-TNF therapy.
Patrick Kiely	Consultancy, honoraria for lecturing for: Schering-Plough Roche Bristol-Myers Squibb	None	None	Medical advisor for National Rheumatoid Arthritis Society (NRAS)
Chris Deighton	None	None	My department has received sponsor-ship for meetings and unrestricted research grants from Wyeth, Abbott and Schering-Plough	My wife is a sales representative for Novartis.
Isabel Raiman	None	None	None	None
Ailsa Bosworth	None	None	NRAS has received educational grants from Roche, Schering-Plough, Abbott, Wyeth, and very small grants from UCB and Bristol-Myers Squibb.	None
Alison Hammond	None	None	None	None
Jonathan Tosh	None	None	None	None

continued

Group member	Personal pecuniary interest	Personal family interest	Non-personal pecuniary interest	Personal non-pecuniary interest
Jane Hall	None	None	None	None
Enid Quest	None	None	None	None
David Morgan	None	None	None	None
Sheena Hennell	None	None	None	None
Michael Rudolf	None	None	None	None
Colin Howie	None	None	None	None
Andrew Robinson	Education contract: de Puy, Johnson & Johnson (non specific). Consultancy contract: Orthomimetics Ltd (non specific); Glaxo SmithKline shareholding (non specific).	None	None	None
Anthony Redmond	None	None	None	None