

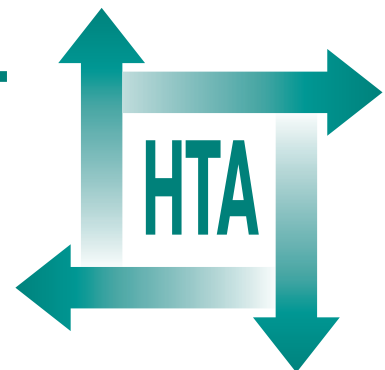
## **The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis**

P Barton, P Jobanputra, J Wilson,  
S Bryan and A Burls



March 2004

**Health Technology Assessment  
NHS R&D HTA Programme**





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## Abstract

### The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis

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**Objectives:** To address the structural issues relating to mortality and quality of life (QoL) effects and to identify data on the general pattern of QoL of rheumatoid arthritis (RA) patients through a restructured and enhanced version of the Birmingham Preliminary Model (BPM).

**Data sources:** Electronic databases and a postal survey of current UK rheumatological practice.

**Review methods:** The focus for this report was to evaluate two new drugs, etanercept and infliximab [antibodies against tumour necrosis factor (anti-TNFs)], for use in the treatment of RA using the Birmingham Rheumatoid Arthritis Model (BRAM). Having carried out a rapid systematic review of physician surveys of current disease-modifying antirheumatic drugs (DMARDs) usage patterns in adult patients with RA and a postal survey of consultant rheumatologists working in the UK, the drug sequences were then identified for the model. A series of analyses were then run using the model. The issue of specifying the correct comparison in the analysis being undertaken was investigated using two separate analyses: the situation of comparing anti-TNFs with placebo, and the comparison of a sequence using anti-TNFs with a sequence that represents current practice in the UK.

**Results:** Results from the survey of rheumatologists highlighted the fact that RA has different manifestations and responds to different agents in different patients, all of which makes any summary of practice difficult to achieve and open to the criticism of being an oversimplification. However, the findings generally agree with other surveys and trends observed, such as the increasing acceptance of methotrexate as first line drug of choice in patients with RA, especially if the disease is of an aggressive nature. The newer anti-TNF agents have also begun to be incorporated into use. The incremental cost-effectiveness ratios resulting from

the use of an inappropriate comparator of placebo were consistently lower than in the base case where appropriate comparator drugs sequences are used. The focus of the BRAM on a drug sequence helped to avoid the incremental cost-effectiveness of new treatments appearing lower than they really are when inappropriate comparators are used. To test the effect on the analysis results of using the disease-modifying antirheumatic sequence that represents current UK practice, the BRAM was run for the strategies representing current UK practice. The results were not very different from the base-case results.

**Conclusions:** The main achievement of this work was to bring about a more realistic modelling of real-life clinical pathways and events, as it has developed from the BPM to the BRAM. This has been brought about by overcoming structural and data limitations. In addition, the modelling approach reflected in the BRAM is applicable to other chronic conditions, especially those where a sequential approach to therapeutic options exists. The model has been successfully restructured so that different sequences of treatment can readily be considered, including the sequence that best represents current clinical practice in the UK. In addition, the flexibility inherent in using a modelling approach to consider these health policy questions has been demonstrated. One of the key uncertainties that can now be explored concerns the impact of new drugs on disease progression. Current evidence on this is weak, but should new agents demonstrate such a benefit then the BRAM may be a suitable vehicle through which to investigate the costs and full effects. Inevitably, there remain problems and limitations with the BRAM, but these are almost entirely data limitations. As data on these issues become available the BRAM provides a convenient tool through which reanalysis might be undertaken.





# Contents

<b>List of abbreviations</b> .....	vii	<b>Acknowledgements</b> .....	37
<b>Executive summary</b> .....	ix	<b>References</b> .....	39
<b>1 Introduction</b> .....	1	<b>Appendix 1</b> Search strategy for DMARD use systematic review .....	43
Background .....	1	<b>Appendix 2</b> Summary of survey papers .....	45
The clinical problem, drug treatments and evidence on effectiveness .....	2	<b>Appendix 3</b> Current treatment practice using DMARDs .....	51
Outline of BPM .....	2	<b>Appendix 4</b> The Delphi version of the BRAM .....	55
Limitations of the BPM .....	3	<b>Appendix 5</b> Sampling from conditional distributions .....	75
Purpose of this report .....	4	<b>Appendix 6</b> Details of published data about HAQ changes for DMARDs .....	77
<b>2 Determining current UK patterns of DMARD usage</b> .....	5	<b>Appendix 7</b> Health Assessment Questionnaire (HAQ) .....	79
Rapid systematic review of physician surveys of current DMARD usage patterns in adult patients with RA .....	5	<b>Appendix 8</b> ACR classification of functional status in RA .....	81
Survey .....	7	<b>Appendix 9</b> Regression analysis of QoL against HAQ .....	83
Conclusions on DMARD use .....	11	<b>Appendix 10</b> Rapid review of effect of joint replacement on HAQ .....	85
<b>3 The Birmingham Rheumatoid Arthritis Model (BRAM)</b> .....	13	<b>Appendix 11</b> BRAM simulation model results .....	89
Introduction to the BRAM .....	13	<b>Health Technology Assessment reports published to date</b> .....	93
Basic principles of the model .....	13	<b>Health Technology Assessment Programme</b> .....	101
Data used in the BRAM .....	19		
QoL and mortality .....	21		
Details of event and activity handling .....	24		
Validation comparison of BRAM and BPM .....	25		
<b>4 Results</b> .....	27		
BRAM base-case results .....	27		
Variation in comparators .....	27		
Flexibility of the BRAM .....	28		
<b>5 Discussion</b> .....	33		
Main findings and generalisability of approach .....	33		
Strengths and limitations of the BRAM .....	34		
Priorities for further research .....	35		







## List of abbreviations

ACR	American College of Rheumatology	EMEA	European Agency for the Evaluation of Medicinal Products
AKA	anakinra	EQ-5D	EuroQol EQ-5D quality of life questionnaire
anti-TNF	antibodies against tumour necrosis factor	ESR	erythrocyte sedimentation rate
AZA	azathioprine	Etan	etanercept
AUR	oral gold	FBC	full blood count
BP	blood pressure	GI	gastrointestinal
BPM	Birmingham Preliminary Model	GST	injectable gold
BRAM	Birmingham Rheumatoid Arthritis Model	HAQ	Health Assessment Questionnaire
BSR	British Society for Rheumatology	HCQ	hydroxychloroquine
CHL	chloroquine	ICER	incremental cost-effectiveness ratio
CI	confidence interval	IL-1ra	interleukin-1 receptor antagonist
Comb	combination therapy with two or more DMARDs	i.m. or IM	intramuscular
CPMP	Committee for Proprietary Medicinal Products	Infl	infliximab
CRP	C-reactive protein	ITT	intention to treat
CSV	comma-separated value	LEF	leflunomide
CXR	chest X-ray	LFT	liver function tests
CyA	ciclosporin	MTIM	intramuscular methotrexate
DES	discrete event simulation	MTX	methotrexate
DMARD	disease-modifying antirheumatic drug	MYO	intramuscular gold
D-Pen	D-penicillamine	NICE	National Institute for Clinical Excellence
		NSAID	non-steroidal anti-inflammatory drug

*continued*

**List of abbreviations continued**

Pall	palliative treatment	RR	relative risk
QALY	quality-adjusted life-year	SE	standard error
QoL	quality of life	SF-36	Short Form with 36 items
q.s.e.	quasi-standard error of difference in mean (reflecting the uncertainty due to sampling within the model, not the parameter uncertainty)	SMR	standardised mortality ratio
RA	rheumatoid arthritis	SSZ	sulfasalazine
RCT	randomised controlled trial	TNF- $\alpha$	tumour necrosis factor- $\alpha$
RF	rheumatoid factor	U&E	urea, electrolytes and creatinine
		WMHTAC	West Midlands Health Technology Assessment Collaboration

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



## Executive summary

### Background

Using effectiveness data from trials where the comparator does not reflect current clinical practice may give a misleading impression of the incremental cost-effectiveness of the new technology in question. This is likely to be a particular problem for treatments for chronic diseases, where the clinical pathway is often complex, and for which appropriate comparative data tend to be limited. The focus for this report was to evaluate two new drugs, etanercept and infliximab [antibodies against tumour necrosis factor (anti-TNFs)], for use in the treatment of rheumatoid arthritis (RA). The comparators in the trials of anti-TNFs tend to be placebo and so do not reflect clinical practice. Earlier work by the authors resulted in the development of a preliminary model that was used to overcome the limitations of the trial data. That work showed that decision analytic models based on estimates of the effectiveness of the drug directly derived from the trial data were inadequate representations of real-life clinical practice and potentially resulted in misleading estimates of the incremental cost-effectiveness. This report takes forward this work by exploring ways of avoiding the use of inappropriate comparators through the use of suitably flexible modelling techniques. The modelling approach described here is potentially applicable to other conditions, especially those where a sequential approach to therapeutic options exists.

### Objectives

The main objective of the research reported here was to overcome some of the identified limitations of the Birmingham Preliminary Model (BPM). Thus, the study sought to address the structural issues relating to mortality and quality of life (QoL) effects and to identify data on the general pattern of QoL of RA patients. The aim was to restructure the model so that different sequences of treatment could be considered, and to determine the sequence that best represents current clinical practice in the UK. An additional aim was to demonstrate the flexibility inherent in

using a modelling approach to consider these health policy questions.

### Methods

The preliminary model used in the earlier review, the BPM, was developed further in the work reported here. The Birmingham Rheumatoid Arthritis Model (BRAM) is essentially a substantially revised and extended version of the BPM. Some of the most significant changes from the BPM are listed below.

- The BRAM describes the current state of a patient in terms of Health Assessment Questionnaire (HAQ) score, rather than quality of life more generally.
- Mortality is allowed to depend on HAQ score.
- The BRAM also includes provision for the average rate of increase in HAQ to vary according to treatment.
- There is provision for joint replacement to be included in the analysis; the risk of this again depends on HAQ. However, the model may also be run without consideration of joint replacement.

The newly developed BRAM model is also used to investigate further the limitations of the methods that use clinically inappropriate comparators.

Like the BPM, the BRAM operates as an individual sampling model. This type of model is a form of discrete event simulation in which only one individual is considered at a time. The intention behind this type of model is to produce a realistic set of virtual patient histories, from which estimates of population mean costs and mean effects (e.g. quality-adjusted life-years) can be estimated. This requires consideration of individual variation at all relevant points in the model. Such variation has been incorporated wherever practicable within the limitations of the available data.

To ensure that the model truly reflected modern clinical practice a systematic review of drug use in the treatment of RA and a survey of current practice by rheumatologists in the UK were also undertaken.

## Results

The results from the survey of rheumatologists highlighted the fact that RA has different manifestations and responds to different agents in different patients, all of which makes any summary of practice difficult to achieve and open to the criticism of being an oversimplification. However, the findings generally agree with other surveys and trends observed, such as the increasing acceptance of methotrexate as first line drug of choice in patients with RA, especially if the disease is of an aggressive nature. The newer anti-TNF agents have also begun to be incorporated into use.

One of the central issues explored in this project is the importance of specifying the correct comparison in the analysis being undertaken. This was investigated using two separate analyses: the situation of comparing anti-TNFs with placebo, and the comparison of a sequence using anti-TNFs with a sequence that represents current practice in the UK.

The incremental cost-effectiveness ratios resulting from the use of an inappropriate comparator of placebo were consistently lower than in the base case where appropriate comparator drugs sequences were used. The focus of the BRAM on a drug sequence helped to avoid the incremental cost-effectiveness of new treatments appearing lower than they really are when inappropriate comparators are used. To test the effect on the analysis results of using the disease-modifying antirheumatic sequence that represents current UK practice, the BRAM were run for the strategies representing current UK practice. The results were not very different from the base-case results.

As with any health technology assessment exercise, there remain some potentially important uncertainties in this evaluation work. A major

benefit associated with the adoption of a modelling approach is that the importance of some of the uncertainties can readily be explored. The BRAM was used to demonstrate how the sensitivity of the analysis results to variation in key assumptions and data-based estimates can be explored. The issues investigated include: the effect of joint replacement on HAQ, the assumptions concerning rate of change in HAQ, and the proportions of patients who reach palliation.

## Conclusions

The main achievement of this work was to bring about a more realistic modelling of real-life clinical pathways and events, as it has developed from the BPM to the BRAM. This has been brought about by overcoming structural and data limitations. In addition, the modelling approach reflected in the BRAM is applicable to other chronic conditions, especially those where a sequential approach to therapeutic options exists. The model has been successfully restructured so that different sequences of treatment can readily be considered, including the sequence that best represents current clinical practice in the UK. In addition, the flexibility inherent in using a modelling approach to consider these health policy questions has been demonstrated. One of the key uncertainties that can now be explored concerns the impact of new drugs on disease progression. Current evidence on this is weak, but should new agents demonstrate such a benefit then the BRAM may be a suitable vehicle through which to investigate the costs and full effects.

Inevitably, there remain problems and limitations with the BRAM, but these are almost entirely data limitations. As data on these issues become available the BRAM provides a convenient tool through which reanalysis might be undertaken.

# Chapter I

## Introduction

### Background

To make informed decisions about the appropriate use of treatments and technologies in the health service it is necessary for decision-makers to have access to the current best available evidence, not only about the effectiveness, but also about the cost-effectiveness of a technology. It is important for decision-makers to know the incremental cost-effectiveness of the technology, that is, what is the change in cost and the change in effectiveness achieved by using this technology compared with current practice.

Although it has been argued on ethical grounds that randomised controlled trials (RCTs) should compare new treatments against standard practice, many new drugs are only compared with placebo in clinical trials. Moreover, this is likely to continue as it is the explicit policy of the European Agency for the Evaluation of Medicinal Products (EMA):

“Forbidding placebo-controlled trials in therapeutic areas where there are proven prophylactic, diagnostic or therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest. ... Provided that the conditions that ensure the ethical nature of placebo-controlled trials are clearly understood and implemented, it is the position of the CPMP [Committee for Proprietary Medicinal Products], and the EMA that continued availability of placebo-controlled trials is necessary to satisfy public health needs.”<sup>1</sup>

However, using effectiveness data directly taken from such trials (where the comparator does not reflect current clinical practice) to populate a decision analytic model may give a misleading impression of the incremental cost-effectiveness of a new technology. If a treatment is simple and of short duration, then using methods of indirect comparison of the effectiveness may be a possible approach to obtaining incremental effectiveness estimates and overcoming the limitations of the trial data. However, this is not always possible: there are many chronic diseases, often with complex clinical pathways, for which appropriate data for comparisons are limited. Rheumatoid arthritis (RA) is one such chronic disease.

In 2001 the West Midlands Health Technology Assessment Collaboration (WMHTAC) at the University of Birmingham was commissioned to produce a rapid technology assessment of two new drugs, etanercept and infliximab [known as antibodies against tumour necrosis factor (anti-TNFs)], for use in the treatment of RA. The assessment was undertaken to inform the appraisal process of the National Institute for Clinical Excellence (NICE).<sup>2</sup>

This assessment of anti-TNFs in RA exemplified the kind of problems facing decision-makers, described above, for the following reasons.

- RA is a chronic, usually lifelong, condition.
- There are many treatment options currently available for the population of RA patients for whom an anti-TNF is indicated.
- ‘Do nothing’ is not a treatment that, other things being equal, would be considered ethically acceptable by rheumatologists.
- Current treatments have different effectiveness, costs and adverse event profiles.
- Patients are often treated sequentially or concurrently with different drugs.
- The comparators in the trials of anti-TNFs did not at that time reflect the clinical practice in that they were predominantly against placebo.

In the 2001 technology assessment report the present researchers tried to overcome the limitations of the trial data through the application of a modelling approach.<sup>2</sup> Given the short time-frame and the limited availability of existing data, the health economic and modelling components of the work were necessarily limited in scope. However, the work was sufficient to show that decision analytic models based on estimates of the effectiveness of the drug directly derived from the trial data that compare the new drug to placebo were inadequate representations of real-life clinical practice and potentially resulted in misleading estimates of the incremental cost-effectiveness.

This report takes forward this work by exploring ways of avoiding the use of inappropriate comparators through the use of suitably flexible modelling techniques. The modelling approach

described here is potentially applicable to other conditions, especially those where a sequential approach to therapeutic options exists. The preliminary model used in the rapid review (hereafter referred to as the Birmingham Preliminary Model or BPM) is developed further and its sensitivity to factors, such as mortality, joint replacement and quality of life (QoL) explored. The developed model (hereafter referred to as the Birmingham Rheumatoid Arthritis Model or BRAM) is used to investigate further the limitations of the methods that use clinically inappropriate comparators.

To ensure that the model truly reflects modern clinical practice, a systematic review of drug use in the treatment of RA and a survey of current practice by rheumatologists in the UK were also undertaken for this report. The methods and results of this survey are reported in Chapter 2.

## The clinical problem, drug treatments and evidence on effectiveness

RA is a chronic illness characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. Key aims of treatment include:

- control of joint pain and inflammation
- reduction in joint damage and disability
- improvement in physical function
- maintenance of or improvement in QoL.

Drugs that have been shown to inhibit, or have the prospect of inhibiting joint destruction are known as disease-modifying antirheumatic drugs (DMARDs). There are around eight DMARDs currently in common use in the UK. These drugs are not always effective, can lose effectiveness with time and can cause adverse effects. This leads to a low likelihood of long-term use of a single drug for a disease with a lifelong course. New DMARDs are therefore of great importance and several new agents have appeared in recent years.

Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a cytokine that plays an important role in mediating joint inflammation. Its actions may be inhibited by infliximab (Remicade<sup>®</sup>, Schering-Plough), a monoclonal antibody that binds to soluble and cell-bound TNF- $\alpha$ , and by etanercept (Enbrel<sup>®</sup>; Wyeth-Ayerst), a synthetic receptor for TNF- $\alpha$ . Both agents are licensed for use in the UK for the treatment of RA. Infliximab is given by

intravenous infusion at 0, 2 and 6 weeks and at 8-weekly intervals thereafter. It is only licensed for use concomitantly with methotrexate. Etanercept is given by twice-weekly subcutaneous injection and can be given for an indefinite period. There are several other new biological agents for use in RA under development.

At the time of producing the 2001 technology assessment, there were six RCTs of etanercept in patients with RA, involving a total of 1710 patients (1230 of whom received etanercept). Five of these trials compared etanercept with placebo and one compared etanercept with methotrexate. There were four RCTs of infliximab in patients with RA, involving 630 patients (497 of whom received infliximab). All compared infliximab with placebo. The trials were of good quality. They demonstrated that both etanercept and infliximab improve the outcomes in adults with RA when compared with placebo. The only trial that compared an anti-TNF agent with a DMARD (etanercept compared with methotrexate) failed to demonstrate a convincing treatment difference between them.

## Outline of BPM

The BPM was constructed using TreeAge DATA 3.5. It follows patients with RA from the time at which they first start using DMARDs. As RA is usually a lifelong condition, the BPM assumes that a DMARD would be used for the remainder of that patient's life, if it is not stopped because of lack of effectiveness or toxicity. If a drug is stopped it assumes that the patient will be started on another DMARD.

When the model is run, a large number of individual (virtual) patient histories are generated. The patients follow a sequence of DMARDs chosen to reflect a typical clinical pathway. The model is structured so that a patient follows a pathway both with and without the addition of the new anti-TNF. As in clinical practice, patients switch to the next DMARD in the sequence when the current DMARD is ineffective or produces toxicity.

The mean costs and quality-adjusted life-years (QALYs) for the two arms of the model are compared to produce an incremental cost-effectiveness ratio (ICER).

A decision was made not to use a standard Markov model because such an approach has certain characteristics that constrain its flexibility.

1. Transition probabilities are independent of time spent in the current state.
2. Transition probabilities are independent of states visited before the current state.
3. Events are timed to multiples of a fixed cycle time.

The BPM uses tracker variables to overcome some of the inherent restrictions of Markov models. Tracker variables enable a patient's clinical course to be influenced by how long the patient has been on a particular drug and be related to their past medical history, thereby overcoming restrictions 1 and 2. The novel use of tracker variables to overcome restriction 3 not only permits events to occur at any time, but also increases computational efficiency, as the model does not have to draw repeatedly from a random number generator for patients simply to stay in the same state.

The purpose of the preliminary model was to assess the incremental cost-effectiveness of using anti-TNFs to treat patients with RA, not to assess different orders of using other DMARDs, so a fixed order, reflecting acceptable clinical practice, was chosen for the 'without anti-TNF' branch.

The DMARD sequence used was:

1. sulfasalazine (SSZ)
2. methotrexate (MTX)
3. gold (GST)
4. azathioprine (AZA)

5. D-penicillamine (D-Pen)
6. hydroxychloroquine (HCQ)
7. leflunomide (LEF)
8. ciclosporin (CyA).

Any patient who has lived long enough and failed on all the above DMARDs then receives combination therapy (Comb) consisting of CyA plus MTX, provided that neither of these has proved toxic to them in the past. After combination therapy, or if combination therapy could not be given, patients receive palliative treatment (Pall). *Figure 1* shows the patient pathways in the model.

The model was populated with data concerning:

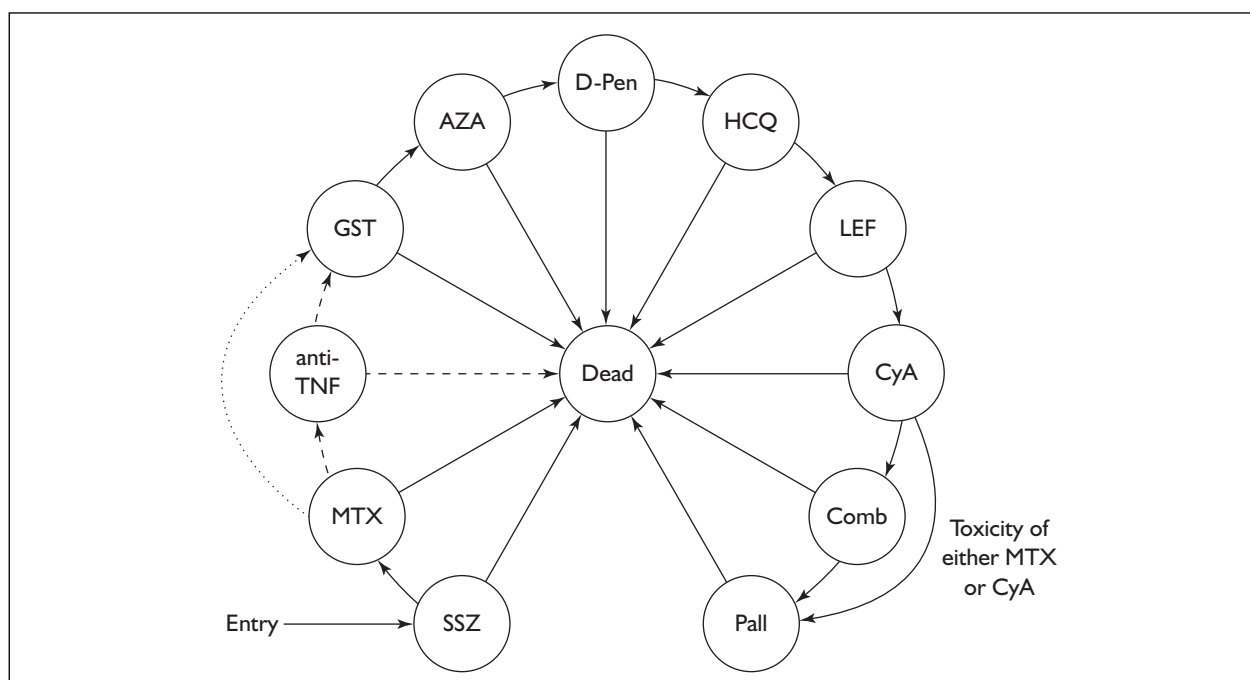
- each patient's life expectancy
- time spent on each DMARD
- costs and QoL effects associated with treatment.

A simplifying assumption was made that QoL effects of all DMARDs, other than SSZ, MTX and anti-TNFs, were the same.

Further details of the model and its provisional results are contained in the original report.<sup>2</sup>

## Limitations of the BPM

As indicated in the earlier report on the BPM,<sup>2</sup> there existed both structural and data limitations



**FIGURE 1** Patient pathway in the BPM

that required further work if the model was to have a high level of descriptive validity.

The main structural problems with the BPM relate to limitations on the scope of the model. For example, the BPM assumes a fixed pattern of effect of DMARDs on QoL and this assumption prevents the model from allowing for mortality effects. Clearly, the failure of the BPM to consider the effects of DMARDs on mortality is important in that the inclusion of this factor could potentially have a major effect on the model results. Additional concerns regarding model scope relate to the fact that the model does not consider the effect of DMARDs on disease progression, joint replacement or hospitalisation. A further structural limitation of the BPM is that the model assumes a fixed order for the DMARDs apart from anti-TNFs. The model does not incorporate the flexibility to vary the order in which DMARDs are used.

A key parameter in the BPM is time spent on each DMARD. In the earlier analysis, estimates for this parameter for each DMARD were obtained by fitting a curve to a limited number of data points and extrapolating the fitted curve beyond the data. This represents an important data limitation in the BPM results reported previously. Other data

limitations concern costs and QoL. The costing data were obtained from a limited range of sources and the QoL effects of DMARDs were estimated from very limited data on changes in Health Assessment Questionnaire (HAQ) score. The HAQ is a commonly used disability index in RA. Finally, no data on the general pattern of QoL of RA patients were included in the model analysis.

## **Purpose of this report**

In bold terms, the purpose of the work reported here was to build a better model of the clinical management of RA patients. An objective of the research was to overcome some of the identified limitations of the BPM. Thus, the study sought to address the structural issues relating to mortality and QoL effects and to identify data on the general pattern of QoL of RA patients. The aim was to restructure the model so that different sequences of treatment could be considered, and to determine the sequence that best represents current clinical practice in the UK. A further aim was to demonstrate the flexibility inherent in using a modelling approach to consider these health policy questions.



## Chapter 2

# Determining current UK patterns of DMARD usage

Before the model could be constructed adequately, it was necessary to identify the drug sequences to be used in a way that reflects current UK practice for treatment of patients with RA. A rapid review of the current literature on this topic was therefore undertaken. This is reported in the following section. This review revealed that the published evidence was neither sufficiently up to date nor robust for the purposes of the study, so a postal survey of current UK rheumatological practice was undertaken. This is reported in the section 'Survey', below.

### Rapid systematic review of physician surveys of current DMARD usage patterns in adult patients with RA

#### Search strategy

The generic names for currently used DMARDs, together with key terms such as 'data collection', 'questionnaires', 'physician's practice patterns' were used to search EMBASE and MEDLINE for physician surveys reporting patterns of DMARD use (see Appendix 1 for full details of the search). Searches were not restricted by language, but the search date was from 1990 onwards, as up-to-date information was needed to inform the BRAM. Citation lists of included studies were also searched.

#### Inclusion and exclusion criteria

Studies were included if they described:

- a survey of rheumatology physicians that enquired about current DMARD usage and prescribing practice
- questionnaires regarding DMARD prescription to rheumatology physicians based on vignettes using paper patients.

Surveys of non-specialists such as primary care physicians were excluded. Patient surveys and cross-sectional surveys where information was collected from a variety of sources such as drug

registers, patients and treatment records were also excluded.

#### Results

Only eight studies met the inclusion criteria. Four papers asked rheumatologists what their typical prescriptions would be in a patient naive to DMARDs,<sup>3-6</sup> and four had set out scenarios or vignettes using hypothetical patients to try to identify physician prescription differences in different types of patients.<sup>7-10</sup>

There were just six countries from which data were identified: the UK,<sup>3</sup> the USA,<sup>5</sup> Canada,<sup>4</sup> France<sup>7</sup> and Australia with New Zealand.<sup>6</sup>

#### Summary of findings

The percentages of respondents nominating DMARDs are presented.

#### Initial DMARDs prescribed: generic patient

- Kay and Pullar (1992)<sup>3</sup> (UK, survey date unknown)  
Sulfasalazine was the overall drug of preference, other DMARDs such as D-penicillamine, IM gold, methotrexate, oral gold and azathioprine were prescribed initially on occasion.
- Conaghan and co-workers (1997)<sup>6</sup> (Australia and New Zealand)  
In 1994 methotrexate (94%), sulfasalazine (91%) and antimalarials (60%) were the most commonly cited drugs, in contrast to 1984, when gold (94%), D-penicillamine (89%) and antimalarials (54%) were physician preferences.
- Mikuls and O'Dell (2000)<sup>5</sup> (USA, survey date 1999)  
Methotrexate (64%) and hydroxychloroquine (30%), were the most preferred DMARDs, with sulfasalazine (5%), IM gold and leflunomide (<1%) being preferred by a few.
- Pope and co-workers (2002)<sup>4</sup> (Canada, survey date 2001)  
Methotrexate (100%), hydroxychloroquine (100%), sulfasalazine (98%), combination (80%) and IM gold (40%) were the most commonly preferred DMARDs, with chloroquine (16%), azathioprine (9%), ciclosporin (6%), D-penicillamine (2%) and oral gold (1%) also being used.

**Initial DMARDs prescribed: data elucidated from vignettes**

- Collins and co-workers (1994)<sup>9</sup> (Canada, survey date 1992)  
Scenarios 1–5 described patients of increasing severity.
  - *Scenario 1*: IM gold (35.5%), hydroxychloroquine (28.4%), methotrexate (18.7%), sulfasalazine (9%), combination – hydroxychloroquine + IM gold (1.9%), oral gold (1.3%).
  - *Scenario 2*: hydroxychloroquine (51%), IM gold (16.1%), methotrexate (16.1%), sulfasalazine (13.5%), combination – hydroxychloroquine + methotrexate (1.9%), combination – hydroxychloroquine + sulfasalazine (0.6%).
  - *Scenario 3*: IM gold (36.4%), methotrexate (35.1%), hydroxychloroquine (14.9%), sulfasalazine (5.8%), combination – hydroxychloroquine + IM gold (5.2%), D-penicillamine (0.6%), combination – IM gold + methotrexate (0.6%).
  - *Scenario 4*: Methotrexate (34.9%), IM gold (34.2%), hydroxychloroquine (19.7%), sulfasalazine (5.3%), combination – hydroxychloroquine + IM gold (2%), oral gold (1.3%), D-penicillamine (1.3%), combination – hydroxychloroquine + methotrexate (1.3%).
  - *Scenario 5*: Methotrexate (44.5%), IM gold (31.6%), combination – hydroxychloroquine + IM gold (5.2%), combination – IM gold + methotrexate (4.5%), sulfasalazine (2.6%), triple combination – hydroxychloroquine + methotrexate + IM gold (1.3%), D-penicillamine (0.6%), combination – oral gold + methotrexate (0.6%), combination – azathioprine + methotrexate (0.6%), triple combination – hydroxychloroquine + methotrexate + sulfasalazine (0.6%).
- Erkan and co-workers (2002)<sup>10</sup> (USA, survey date 2000)
  - Mild disease: hydroxychloroquine.
  - Moderate/severe disease: methotrexate.
- de Asit and co-workers (1996)<sup>7</sup> (France, survey date 1994)
  - Sequences
  - Case 1: multiple prognostic factors; IM gold (55%), methotrexate (25%), tiopronin (9%), hydroxychloroquine (7%), D-penicillamine (4%), sulfasalazine (2%). If deterioration occurred at 1 year most moved to methotrexate (65%).
  - Case 2: poor socio-economic situation, hydroxychloroquine (42%), IM gold (37%), tiopronin (7%), sulfasalazine (7%), methotrexate (6%). If stable at 1 year, IM

- gold (41%), methotrexate (18%), hydroxychloroquine (4%); if improved at 1 year continued same prescription.
- Case 3: severe inflammation, 80 years old; IM gold (45%), hydroxychloroquine (24%), sulfasalazine 12%, methotrexate 10%, tiopronin (5%), D-penicillamine (4%). Stable at 1 year, IM gold (35%), methotrexate (24%), hydroxychloroquine (13%), sulfasalazine (10%), D-penicillamine (6%); if improved at 1 year similar DMARDs to presentation.
- Maetzel and co-workers (1998)<sup>8</sup> (USA and Canada, survey date 1996)  
Three scenarios: scenario 1 = aggressive RA; scenario 2 = moderate RA; scenario 3 = aggressive RA failing 25 mg methotrexate.
  - *Scenario 1*: (Canada survey): aggressive RA, methotrexate (68.7%), gold (14.5%).
  - *Scenario 1* (USA survey): methotrexate (78.5%).
  - *Scenario 2* (Canada survey): moderate RA, hydroxychloroquine (47.2%), methotrexate (22%), gold (11.2%), sulfasalazine (7.9%).
  - *Scenario 2* (USA survey): hydroxychloroquine (39%), methotrexate (38.8%).
  - *Scenario 3* (Canada survey): combination therapy – methotrexate + hydroxychloroquine (41.1%), IM gold (34.6%), combination – methotrexate + IM gold (16.4%)
  - *Scenario 3* (USA survey): combination (38.3%), triple therapy (23.8%), most combinations had methotrexate + either sulfasalazine (11.7%) or hydroxychloroquine (11.7%), triple therapy had methotrexate + hydroxychloroquine + sulfasalazine.

**Summary of results**

The literature suggests that time of survey, place of survey and disease severity investigated are factors influencing reported prescribing practice. Respondents to surveys undertaken in the USA,<sup>5</sup> Canada<sup>9</sup> and France<sup>7</sup> before 1996 tended to favour IM gold as an initial drug, with methotrexate being used if disease severity increases.<sup>9</sup> After 1996, methotrexate tended to be favoured with hydroxychloroquine a frequently cited drug for mild disease in the USA and Canada.<sup>4,5,8,10</sup> In Australia and New Zealand,<sup>6</sup> IM gold and D-penicillamine were drugs of choice in 1984, superseded by methotrexate and sulfasalazine in 1994. Only one published survey from the UK<sup>3</sup> was found. Published in 1992, it found that sulfasalazine was overwhelmingly the drug of choice at that time.

Fuller details of the papers reviewed are provided in Appendix 2.

## Survey

### Methods

#### Questionnaire

A postal survey of consultant rheumatologists working in the UK was undertaken. The British Society for Rheumatology (BSR) list of ordinary members from the 2001 directory was used to identify practising specialists. Trainees and those in paediatric practice were excluded from this survey because only the practice of established specialists with significant experience of treating adults was of interest. The questionnaire was developed by detailed discussion with colleagues and piloted locally. The final questionnaire examined three main areas: DMARD(s) of first choice, typical DMARD sequence in a patient who fails to respond or has adverse effects to a DMARD, and factors that might influence the choice of DMARD. The full questionnaire used is contained in Appendix 3. Rheumatologists were told that the survey sought a 'snapshot' of current practice and that their responses should reflect practice within "current constraints, rather than what you would consider ideal treatment".

Rheumatologists were asked, in a series of questions, what factors influenced treatment patterns. These were: rheumatoid factor status, presence of erosions at diagnosis, number of joints involved, episodic versus persistent disease, need for rapid symptom control (e.g. due to patient distress, job context, social role), manual versus sedentary occupation, drug cost, a high acute-phase reaction, side-effect profile of drug, and age of patient. Respondents were asked to indicate whether they strongly agreed, agreed, were neutral, disagreed or strongly disagreed that these factors influenced their DMARD choice. If they agreed, comments were invited. Respondents were also asked to suggest any other factors that might influence choice and were asked to give their year of graduation.

The survey was mailed in May 2002 with a covering letter on headed paper from the Birmingham University Department of Public Health and Epidemiology. A prepaid envelope for reply was attached. Those not responding were sent a reminder 1 month later. Questionnaires were numbered to allow identification of non-responders and to facilitate a second mailing, but responses and analysis were entirely anonymous. No payment was offered. All data entries were checked for accuracy by a second person.

#### Analysis

Drug preferences were totalled and choices

compared using a frequency distribution histogram. Sequences were determined by plotting a pathway starting with the most commonly cited first choice drug in the sequence. Handwritten comments were abstracted by a medical secretary and cross-checked for accuracy. Key themes were identified from a sample of responses and applied to all remaining responses with modifications if appropriate. Themes were agreed between researchers by consensus.

## Results

### Response rate

In total, 340 questionnaires were returned (73%). Six were returned where the member was not an appropriate recipient (three individuals were not working as consultants, two were paediatric rheumatologists and one had retired). Two additional questionnaires were returned because the recipient had moved or was not known at the address. One person refused to complete the survey. Thus, 331 completed and usable questionnaires were available for analysis.

### First line DMARD choice

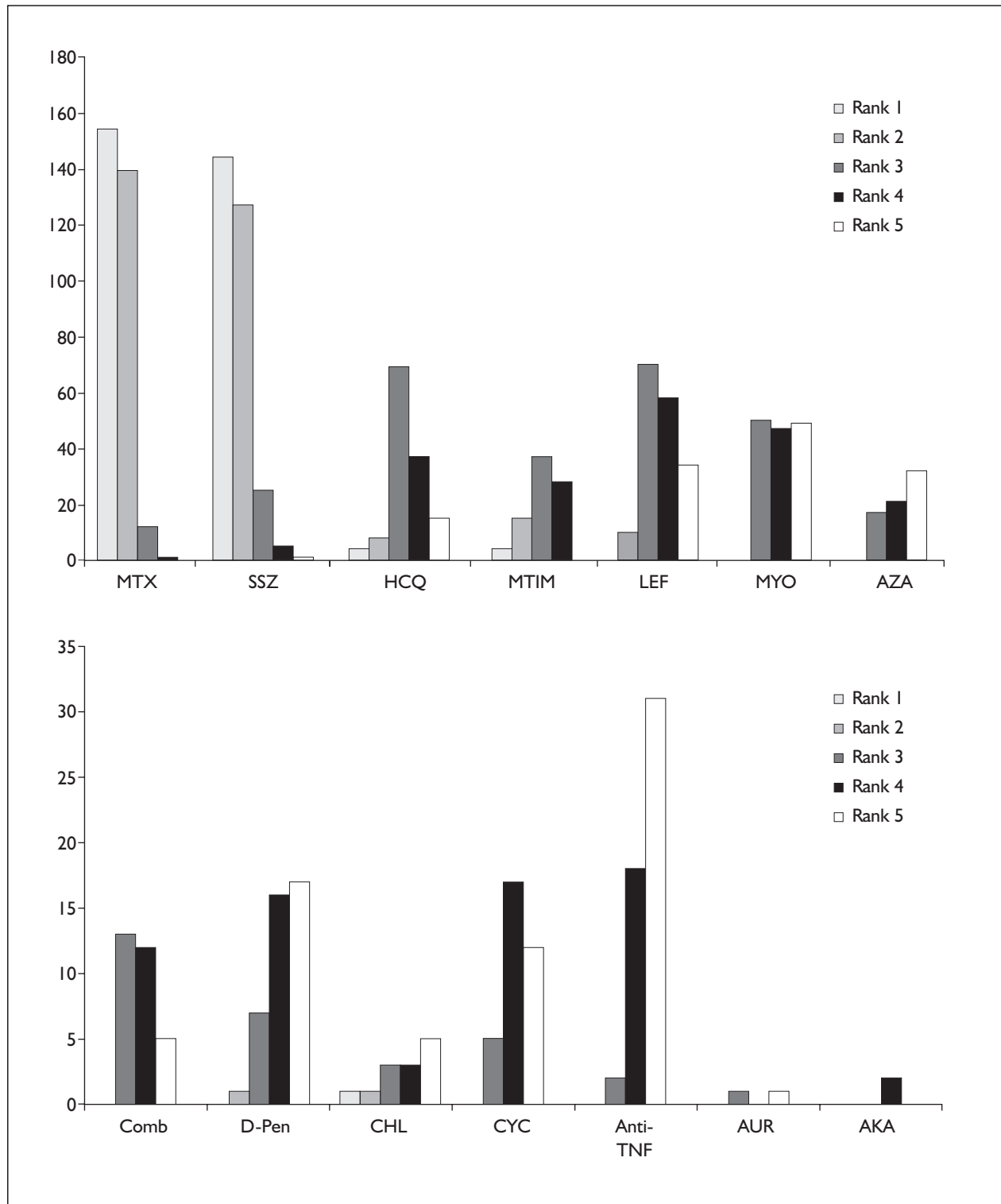
Methotrexate was ranked first by 154 (47%) of rheumatologists and sulfasalazine by 144 (44%). An additional 5% (17/331) ranked methotrexate and sulfasalazine jointly first (*Figure 2*). Of those who ranked methotrexate as first choice, 80% (123/154) ranked sulfasalazine second, and of those who ranked sulfasalazine first, 95% (137/144) ranked methotrexate second. Out of those who ranked methotrexate or sulfasalazine as first choice, 76% and 74%, respectively, estimated that over half of their patients received these drugs.

### DMARD sequences and preferred combinations

Rheumatologists were asked to describe a typical prescribing sequence in patients who fail to respond. The most commonly cited DMARDs were:

- first line drugs: MTX or SSZ
- second line drugs: MTX or SSZ or combination MTX + SSZ
- third line drugs: LEF or MYO or triple combination MTX + SSZ + HCQ
- fourth line drugs: anti-TNF or MYO or AZA
- fifth line drugs: anti-TNF or MYO or AZA or LEF
- sixth line drugs: anti-TNF or MYO or AZA.

Hypothetically, if a sequence started with methotrexate then it could follow that sulfasalazine or a combination of methotrexate + sulfasalazine is the next line of therapy, assuming



**FIGURE 2** Ranking of DMARDs in initial treatment. MTX, methotrexate; SSZ, sulfasalazine; HCQ, hydroxychloroquine; MTIM, IM methotrexate; LEF, leflunomide; MYO, IM gold; AZA, azathioprine; comb, combination; D-Pen, D-penicillamine; CHL, chloroquine; aTNF, anti-TNF; AUR: oral gold; AKA, anakinra.

that the physician has chosen the most popular drugs in his or her sequence. To give an idea of the possible sequences actually chosen in the questionnaire, sequences made up of the most frequently quoted drugs were identified and the number of physicians giving these as their sequences was totalled (*Table 1*).

From this it can be seen that of those choosing methotrexate ( $n = 123$ ) as a first line drug, 42% (52/123) chose sulfasalazine as a second line DMARD, whereas 44% (55/123) favoured a combination of sulfasalazine and methotrexate at this stage. Subsequently, of those choosing the combination of methotrexate and sulfasalazine, 49% (27/55) then added in hydroxychloroquine as a third step. Where single therapies were cited, the most popular sequence was methotrexate, sulfasalazine, leflunomide (34%, 18/52) and anti-TNF therapy (38%, 7/18) as fourth line therapy.

In contrast, of doctors choosing sulfasalazine ( $n = 150$ ) first, 75% (113/150) chose methotrexate and only 12% (18/150) chose sulfasalazine in combination with methotrexate as their second line therapy. Single therapies were more common in those prescribing sulfasalazine as a first line therapy, the most popular sequence being sulfasalazine, methotrexate, leflunomide (30%, 34/113) and either IM gold (50%, 17/34) or anti-TNF (29%, 10/34) as a fourth line therapy.

### **Influences of clinical factors on treatment preferences**

*Table 2* reports the influence of clinical factors on treatment preference. Most of the suggested factors influenced the choice of DMARD. Over 80% of respondents indicated that the presence of erosions at diagnosis influenced DMARD choice and 78% agreed or strongly agreed that drug side-effects also affected choice (*Table 2*). A majority of respondents also agreed, or strongly agreed, that a high acute-phase reaction (66.1%) episodic versus persistent disease (66.1%), and the number of involved joints (67.7%) affected DMARD choice. However, 22% of respondents disagreed, or strongly disagreed, that rheumatoid factor status affected DMARD choice, but 49.1% agreed, or strongly agreed, that it did. Rheumatologists were most commonly neutral with respect to the role of manual versus sedentary occupation in influencing DMARD choice.

### **Analysis of written comments**

#### **Influence of prognostic factors**

There were 56 comments indicating that poor prognostic factors would prompt early use of

DMARDs. Comments such as “use DMARDs with high rheumatoid factor without delay” or “polyarthritis = DMARD” were common. In 102 other comments, the presence of poor prognostic factors suggested influences on DMARD choice and many (347 comments) made reference to the ‘aggressiveness’ of therapy. Often an aggressive intention was specified, for example, “more aggressive treatment if rheumatoid factor positive”. Methotrexate was commonly perceived as drug of choice for aggressive therapy (over 100 comments). Often methotrexate and combination therapy (66 comments) including methotrexate was favoured over sulfasalazine in this setting, for example, “more joints more likely to use methotrexate, all else being equal” or, in response to the presence of erosions at diagnosis, one respondent said “combination and pray”. Fourteen comments referred to anti-TNF therapies, for example, “more aggressive use of more toxic agents – introduce anti-TNF earlier”. By contrast, when referring to episodic versus persistent disease (159 comments), respondents suggested alternative DMARD choices or indicated that episodic disease meant better prognosis, for example, “episodic usually less severe”. Hydroxychloroquine was often preferred for episodic disease (61 comments) and sulfasalazine preferred over methotrexate (41 responses). Four respondents mentioned the use of intermittent steroids with episodic disease. A variety of other comments referred to more general factors, for example, “clinical findings influence me most”, or “X-ray erosions are very misleading”, or missed opportunities in erosive disease (“missed the boat”).

#### **Role of social factors (occupation, fertility and age)**

Occupation did not generally influence the choice of DMARDs. However, some recommended a more aggressive approach for those with manual occupations, for example, “more likely to lose job, therefore quick acting drug”. Another approach was “work advice and probably retraining”. Since only 14.3% of respondents agreed that occupation influenced DMARD choice, and comments were only invited if respondents agreed, there were few comments (34 in total). Twenty comments were made about childbearing and fertility, for example, “caution if potential childbearing age” or wishing to father a child. Avoidance of methotrexate was indicated, “less likely to use methotrexate ...”, or a preference for sulfasalazine or azathioprine, “if of childbearing age may start with sulfasalazine”, or “women considering future pregnancy, more likely to choose azathioprine”. Comments about patient age referred to differences in the goals of therapy

**TABLE 1** Commonly preferred sequences of DMARDs by rheumatologists who specified sulfasalazine or methotrexate as first choice

<b>1st line</b>	<b>Methotrexate (123)</b>						<b>Sulfasalazine (150)</b>						
<b>2nd line</b>	<b>SSZ (52)</b>			<b>MTX+ SSZ (55)</b>			<b>MTX (113)</b>			<b>MTX+ SSZ (18)</b>			
<b>3rd line</b>	<b>LEF (18)</b>	<b>IM Gold (10)</b>		<b>MTX + SSZ +HCQ (27)</b>				<b>LEF (34)</b>	<b>IM Gold (17)</b>	<b>MTX + SSZ +HCQ (4)</b>	<b>IM Gold (2)</b>	<b>MTX + SSZ +HCQ (5)</b>	
<b>4th line</b>	Anti-TNF (7)	LEF (2)	Anti-TNF (1)	Anti-TNF (2)	IM Gold (3)	AZA (1)	Anti-TNF (10)	IM Gold (17)	AZA (1)	AZA (2)	IM Gold (2)	(0)	(0)

Numbers of rheumatologists are shown in parentheses.

**TABLE 2** Factors affecting choice of DMARD

Clinical factor	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Rheumatoid factor status ( <i>n</i> = 328)	9.5%	<b>39.6%</b>	29%	16.5%	5.5%
Erosions at diagnosis ( <i>n</i> = 329)	<b>41.0%</b>	38.9%	10.9%	6.4%	2.7%
Number of joints involved ( <i>n</i> = 328)	20.4%	<b>47.3%</b>	23.2%	7.6%	1.5%
Episodic versus persistent symptoms ( <i>n</i> = 325)	9.8%	<b>56.3%</b>	25.8%	1.5%	6.5%
Need for rapid symptom control ( <i>n</i> = 325)	21.8%	<b>47.7%</b>	20.6%	8.3%	1.5%
Manual versus sedentary occupation ( <i>n</i> = 328)	2.1%	12.2%	<b>61.6%</b>	20.4%	3.7%
Drug cost ( <i>n</i> = 327)	8.3%	26.3%	<b>36.1%</b>	23.5%	5.8%
A high acute-phase reaction ( <i>n</i> = 327)	13.5%	<b>52.6%</b>	24.8%	8.3%	0.9%
Side-effect of profile of drug ( <i>n</i> = 325)	14.8%	<b>63.4%</b>	17.8%	3.4%	0.6%
Age of patient ( <i>n</i> = 325)	4.6%	<b>44.0%</b>	37.5%	11.7%	2.2%

Modal responses are shown in bold.  
*n*, number of responses.

and logistic difficulties in managing elderly patients, for example, “long-term benefits less important than short-term” or “elderly/infirm ... difficulty with bloods would choose sulfasalazine, as monitoring less frequent once established”. A similar approach was suggested for those who have difficulties with blood taking.

#### **Influence of drug toxicity and co-morbidity**

Drug adverse effects were often cited as a factor in DMARD choice, for example, “higher threshold for use, i.e. disease needs to be more active to justify”. Similarly, co-morbidity, smoking habit and alcohol use were also considered, “avoid methotrexate in lung disease”, “reluctant to stop alcohol would not prescribe methotrexate” or “heavy smoker/liver disease (alcoholic) – I won’t use methotrexate. Choice would be IM gold”. Sulfasalazine was also commonly avoided in liver disease and in those who were anti-nuclear antibody positive, “If liver enzymes raised, sulfasalazine and methotrexate not so early” or “if patient is anti-nuclear antibody positive would not use sulfasalazine”. Gold was preferred for those with difficult gastrointestinal symptoms by some rheumatologists, “IM gold if GI problems frequent”. Some comments reflected the complexity of clinical choices, “difficult to answer without writing an essay”.

#### **Influence of drug costs, modes of administration and departmental infrastructure**

Consultants were not generally influenced by drug costs, but a wider perspective was taken in some comments. Safety monitoring of DMARDs was also a consideration in choosing agents, as was the support of nurse specialists, “convenience of monitoring, co-operation by GP, availability of clinical nurse specialist”.

#### **Influence of patient preferences**

There were 43 comments about the patient’s point of view. Some emphasised the importance of patient acceptance of therapies and others reflected patient empowerment through various sources of information.

#### **Conclusions on DMARD use**

There is always a problem about whether surveys reflect actual practice. The results found here are consistent with what has been observed in practice. The facts that RA has different manifestations and responds to different agents in different patients make it complex, and any summary of practice will inevitably be an oversimplification.

The findings generally agree with other surveys and trends observed, such as the increasing acceptance of methotrexate as first line drug of choice in patients with RA, especially if the disease is of an aggressive nature. The newer agents have also begun to be incorporated into use.

Treatments are constantly being introduced and refined in arthritis care, and this survey coincided with the consideration of the TNF inhibitors, etanercept and infliximab, by NICE. In view of the positive guidance that was given on these drugs, rheumatologists in the UK are likely increasingly to use them.

Two DMARD sequences commonly used in the UK were identified for the model. These sequences are given in *Table 16* (see Chapter 4).





## Chapter 3

# The Birmingham Rheumatoid Arthritis Model (BRAM)

### Introduction to the BRAM

The BRAM is essentially a substantially revised and extended version of the BPM.<sup>2</sup> Some of the most significant changes from the BPM are listed below.

- The BRAM describes the current state of a patient in terms of HAQ score, rather than QoL more generally.
- Mortality is allowed to depend on HAQ score.
- The BRAM also includes provision for the average rate of increase in HAQ to vary according to treatment.
- A further new feature is the provision for joint replacement to be included in the analysis; the risk of this again depends on HAQ. However, the model may also be run without consideration of joint replacement.

- etanercept
- gold (GST)
- hydroxychloroquine (HCQ)
- infliximab
- leflunomide (LEF)
- methotrexate (MTX)
- penicillamine (D-Pen)
- sulfasalazine (SSZ)
- combination of MTX and CyA.

Different possible sequences are incorporated in the model by allocating a strategy number to any required sequence of DMARDs. A large number of virtual individuals are then passed through the model. (Pseudo-)random numbers are used as required to determine times spent between events and possible alternative pathways through the model. A pseudo-random number is a number generated by a computer random number generator.

### Basic principles of the model

Like the BPM, the BRAM operates as an individual sampling model. This type of model is a form of discrete event simulation in which only one individual is considered at a time. The intention behind this type of model is to produce a realistic set of virtual patient histories, from which estimates of population mean costs and mean effects (e.g. QALYs) can be estimated. This requires consideration of individual variation at all relevant points in the model. Such variation has been incorporated wherever practicable within the limitations of the data available.

### Patient management strategies and data analysis

#### Strategies

The BRAM can be used to compare the total costs and effects of any desired sequences of DMARD use. In the current form of the model, the DMARDs available are selected from the following list:

- anakinra
- azathioprine (AZA)
- ciclosporin (CyA)

#### Data analysis

The model is designed to compare alternative strategies only from the point of divergence between strategies. For example, in the comparison of two strategies where the first drug (drug A) is common to both but the second drug (used after the failure of drug A) is different, the comparison of mean costs (and QALYs) will exclude costs (and QALYs) experienced by patients while on drug A. Therefore, individuals who do not reach the divergence point do not contribute data to the calculation of mean costs (and QALYs). In effect, the model generates a starting population for the decision problem from a population with incident RA and information about the treatments ahead of the decision point. By contrast, a model that starts at the decision point requires information about the relevant population to be included explicitly.

The model is run separately for each of the strategies being compared. Estimated population mean costs and QALYs are calculated. From these, the mean differences in costs and QALYs, and hence an ICER, are deduced. Because of the stochastic nature of the model, quasi-confidence intervals (CIs) are calculated. These can be

reduced in size by increasing the model sampling size and are quoted to show that a sufficient sampling size has been used.

In line with guidelines from NICE, costs are discounted at 6% per annum and benefits at 1.5% per annum. Costs and QALYs are discounted back to the divergence point and not the start of the patient's experience of RA, as the divergence point represents the time at which the decision between strategies is taken.

A continuous discounting function was used. Thus, a one-off cost  $c$  at time  $t$  (after the point of divergence between strategies) contributes a term  $ce^{-\lambda t}$  to the total discounted cost, where  $\lambda = \ln(1.06)$ . A similar formula is used for the one-off adjustments to total discounted QALYs at start and end of DMARD use, but taking  $\lambda = \ln(1.015)$ .

For the steady-state cost of treatment, the calculation is as follows. Assume that a cost of  $c$

per year applies for  $s$  years starting at time  $t$ . Then the total discounted cost is

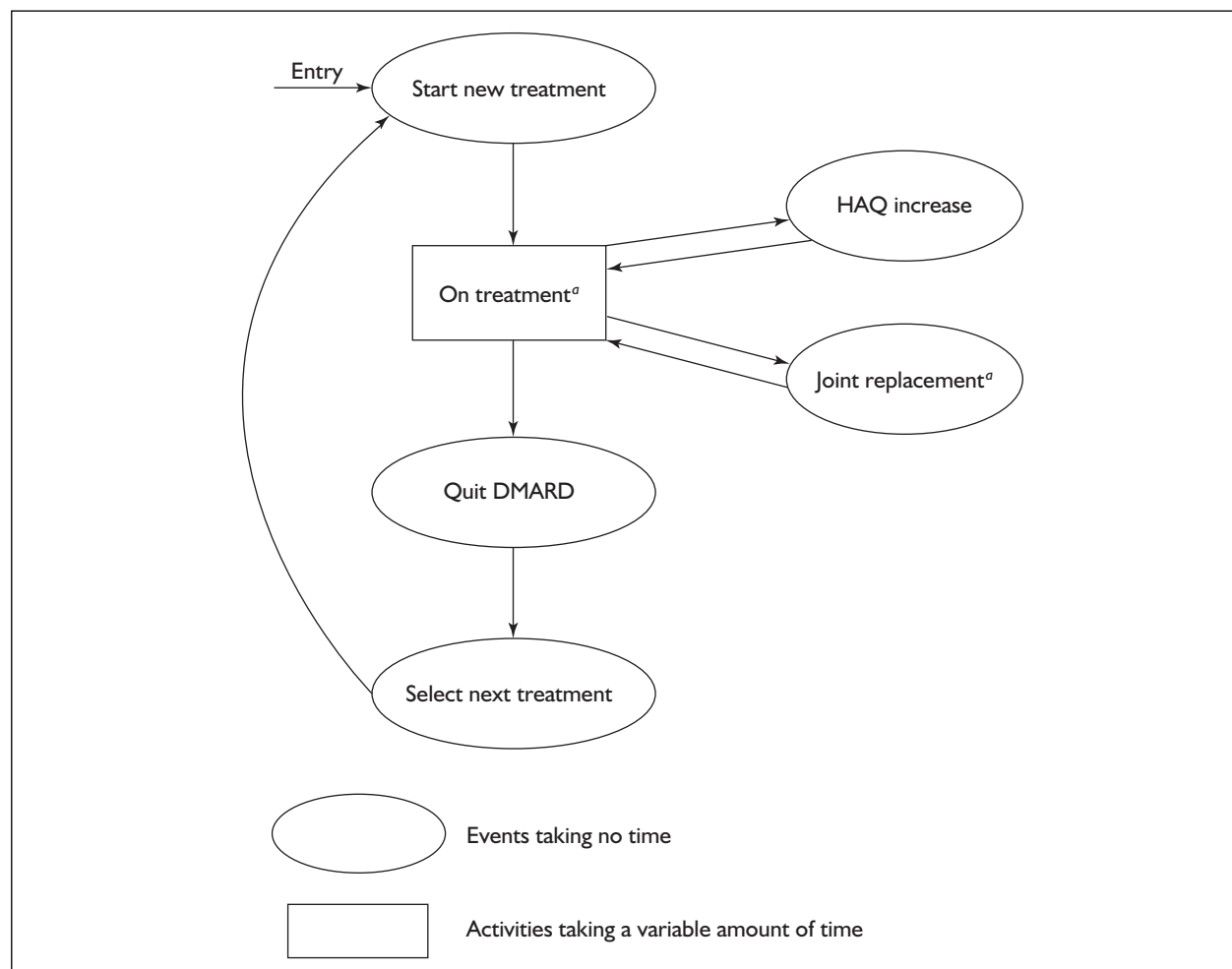
$$\begin{aligned} \int_t^{t+s} ce^{-\lambda\tau} d\tau &= \left[ -\frac{ce^{-\lambda\tau}}{\lambda} \right]_t^{t+s} \\ &= \left( -\frac{ce^{-\lambda(t+s)}}{\lambda} \right) - \left( -\frac{ce^{-\lambda t}}{\lambda} \right) \\ &= \frac{ce^{-\lambda t}}{\lambda} (1 - e^{-\lambda s}) \end{aligned}$$

A similar calculation applies to the QALYs accumulated over a period of constant HAQ score.

### Events and activities

The modelling structure used in the BRAM consists of events (which take no time) and activities (which take a possibly variable amount of time). The events and activities in the BRAM are shown in *Figure 3*.

The main loop is followed for each DMARD successively until no DMARDs remain, when the patient moves to palliation. Joint replacements



**FIGURE 3** Events and activities contained in the model. <sup>a</sup> Patients may die from either of these points.

and HAQ increases interrupt the normal flow through the model. Risk of mortality or need for further joint replacement may be changed. Full details are given later.

### Software used

Two versions of the BRAM were: one in TreeAge DATA Pro and the other in Borland Delphi (see Appendix 4 for source code and further details). The version in TreeAge DATA has the advantage that the logic of the model is open to inspection by the user, whereas the Borland Delphi version runs far more quickly and can thus be used for extensive sensitivity analysis.

In the TreeAge DATA version of the model, the events and activities are coded as states following a Markov node. Tracker variables are used to record all relevant information, including number of DMARDs remaining, total cost and QALYs to date, and time taken. The implicit time-keeping routines within DATA, which assume a constant (and unspecified) time interval between each cycle of the model, are completely bypassed. The structure of this model is substantially different from that of a Markov model; the use of a Markov node is simply the means provided by the software which allows the model to be built. The tree for the full model in TreeAge DATA is shown in *Figure 4*.

In the Borland Delphi version, procedures are used for each event and activity. These are linked through further procedures which ensure that the 'working' procedures are called in the correct order.

### Timing of activities

In the BRAM, time is advanced during the activity 'On treatment'. The activity may be terminated by more than one possible event. Before discussing how such competing risks can be handled, it will be convenient to describe a simpler example. When a patient is to remain in an activity for a given time, and then moves on to a fixed event, the distribution of time in the event can be fully described by a 'survival curve'. The curve is used to convert random numbers to times in the state as illustrated in *Figure 5*. The random number selected is drawn from a uniform distribution between 0 and 1. The inverse of the survival function is applied to this random number to give the time spent in the activity. The inverse survival function may be applied either through a mathematical formula (preferably) or by interpolation between a set of points (if no parametric form for the survival curve is available).

### Competing risks

The activity 'On treatment' can be terminated by any of four events: death, need for joint replacement, HAQ increase, or quitting the DMARD. In modelling these competing risks, it is necessary to establish which reason for termination occurs and the time at which it occurs. There are (at least) four different modelling approaches which can be used: the time-slice approach; determine event first, then time; determine time first, then event; sample times for each possible event and take the minimum. These are described below and the choice of method for the BRAM is explained.

#### **The time-slice approach**

Divide the possible time on the treatment into a number of short intervals (usually equal in length). For each time interval, calculate the probability that each event occurs during that interval. Then draw one number from the random number generator and use it to determine the patient's state at the end of the interval. If the patient has not changed state, this process must be repeated as necessary. See *Table 3* for an example. The actual mapping of a random number to a specific event depends on an arbitrary ordering of the events. Provided that the random numbers are uniformly distributed between 0 and 1, the ordering should not affect the outcome for a large number of patients in a statistically significant way.

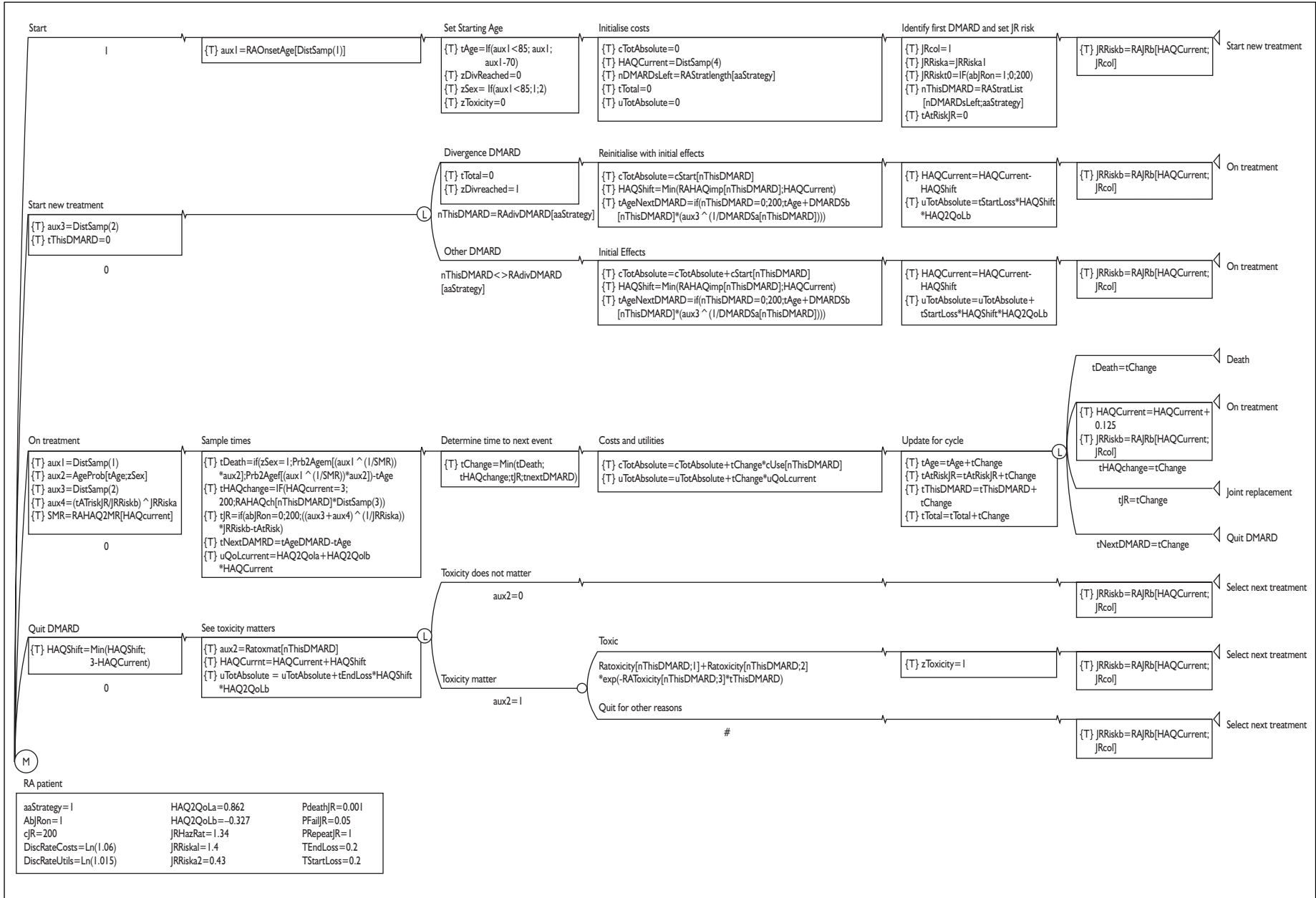
This approach is the one taken in Monte Carlo simulation of Markov chain models, where the probabilities are assumed to be constant over time. In a more general individual sampling model, the probabilities can depend on the patient's individual characteristics and previous history in any way desired.

#### **Determine event first, then time**

First, calculate the overall probability that each of the four possible causes is the reason for ending the activity. Use a random number to select one of those causes. Then use a survival curve appropriate to the given cause to determine the time as described in the previous section.

#### **Determine time first, then event**

For this method, an overall survival curve for the activity is required. Once the time to the event has been determined from one random number, the probability of each possible cause is determined conditional on the time to event. A second random number is then used to determine which event occurs for a particular individual.



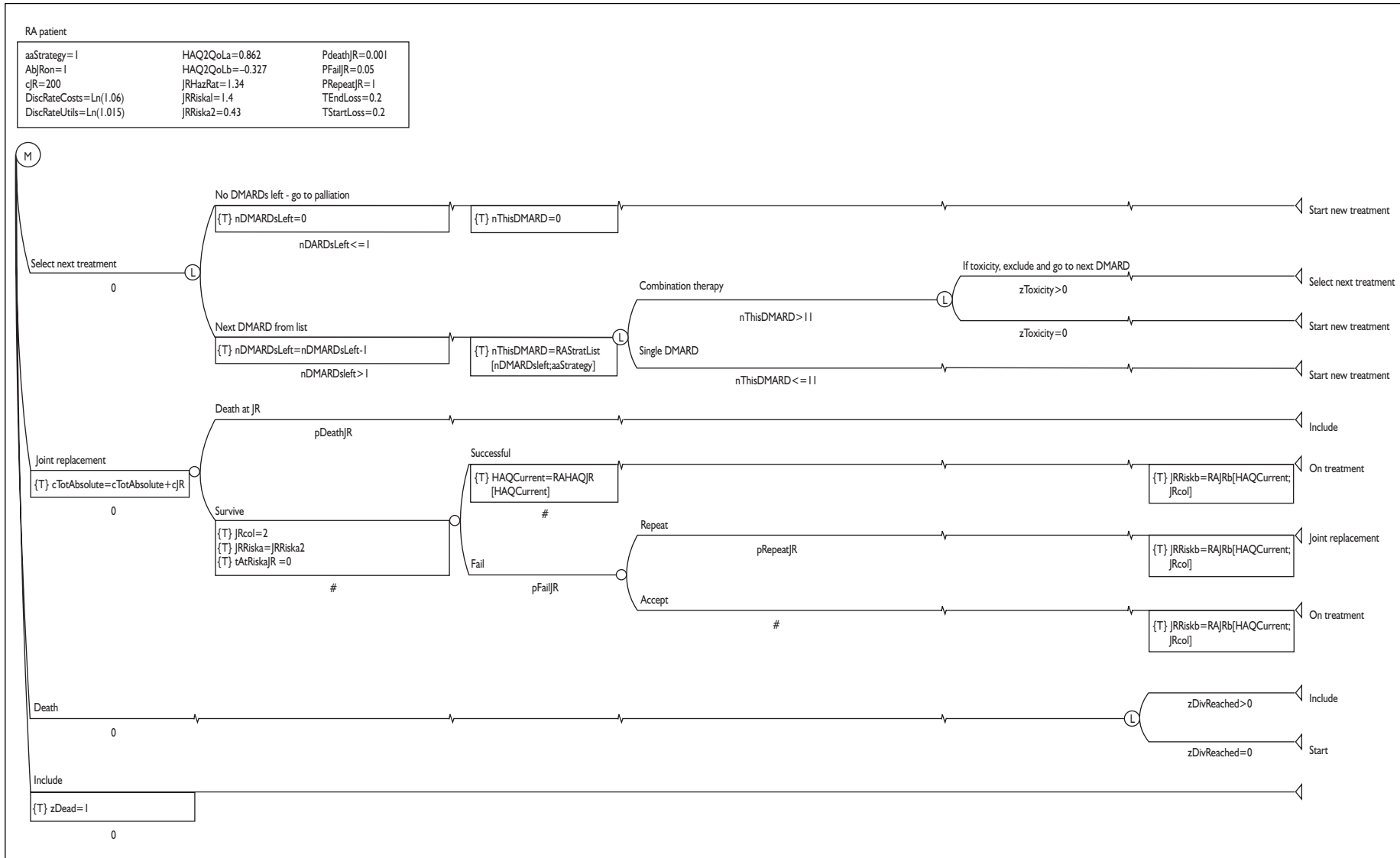


FIGURE 4 Decision analytic tree for the BRAM

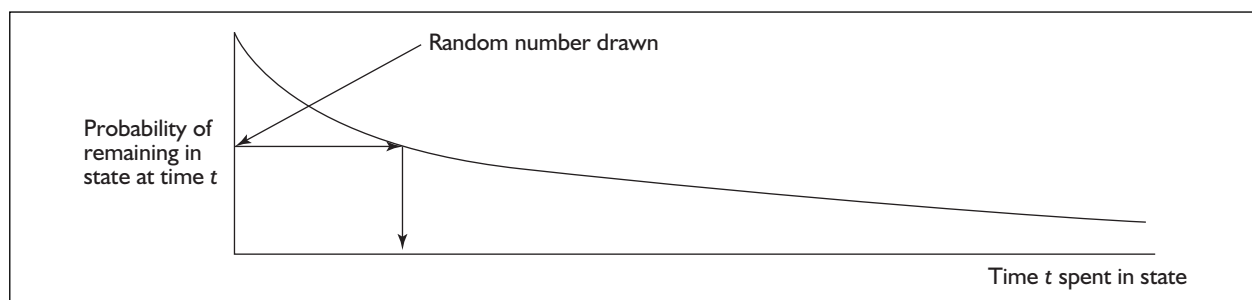


FIGURE 5 Using random numbers with a survival curve

TABLE 3 Illustration of the time-slice approach to handling competing risks

Possible state at end of interval	Probability of moving to that state within interval	Values of random numbers which lead to that option being selected
Death	0.01	0.00 to 0.01
Joint replacement	0.03	0.01 to 0.04
HAQ increase	0.02	0.04 to 0.06
Quitting the DMARD	0.18	0.06 to 0.24
Still on the treatment	0.76	0.24 to 1.00

Note: the probabilities shown here are purely illustrative.

### Sample times for each possible event and take the minimum

Here, what is required for each event is a survival curve assuming that no other event is possible. Then a time is sampled for each event and the earliest time determines which event happens. This is implemented by taking other events as censored events. The other times may be discarded. However, in the case of quitting a DMARD, the time to quitting is not altered by an intervening joint replacement or HAQ change.

### Advantages and disadvantages of the different methods

Although the first method is widely used with Markov models, it has two main drawbacks. First, it only gives the timing of the event to within an interval. This drawback may be overcome by using a further random number to determine the time within an interval. (Alternatively, the precise value of the number already drawn could be used to determine the time: for example, in Table 3 a value just over 0.06 would indicate quitting the DMARD near the beginning of the interval, while a value just under 0.24 would indicate quitting the DMARD near the end.) The implicit assumption that the event is equally likely to occur at any point during the interval is a reasonable approximation to reality if the intervals are short. The second and more serious drawback is that, because the method requires time intervals that are short compared to the time typically spent in the state, the random

number generator must be used many times for each visit to the state. This in turn leads to possibly long running times for the model. A further point is that if the risks of events are not constant, then the probabilities must be recalculated for each cycle, leading to even greater running times.

The remaining three methods are in principle mathematically equivalent. It is simply a matter of converting the data appropriately. In practice, the form in which the data is available may indicate that one method is greatly preferable to the others.

The second method requires the use of at most two calls to the random number generator for the whole activity. (In fact, it can be done with just one random number.) The method depends on easy calculation of the overall probabilities that each event is the actual reason for the end of the activity. If the risk of events depends on the patient's individual characteristics and history, this may not be a sensible approach.

The third method, again, requires only two calls to the random number generator. As with the second method, it may not be easy to calculate overall survival curves if these depend on attributes of the patient.

The fourth method requires one random number for each possible event. It has the advantage that the individual survival curves for the events can be

**TABLE 4** Age and gender percentage distribution used in the BRAM

Age (years)	15–24	25–34	35–44	45–54	55–64	65–74	75–84	Total
Male	2.41	3.51	3.29	8.78	9.76	3.85	2.40	34
Female	4.05	6.07	5.67	16.22	18.02	7.99	7.99	66

calculated independently of each other. This method has been used in the BRAM to separate the competing risks of death, joint replacement, HAQ increase and quitting a DMARD for any cause. However, when a DMARD is potentially part of combination therapy, it is necessary to know whether the DMARD was quit for reasons of toxicity or otherwise. Since this is only required for two of the DMARDs, it is more convenient to use the third method to handle these competing risks.

### Survival distributions used

For death, life tables were used, adjusting for the extra mortality attributable to RA. The extra mortality is a function of the HAQ score of the patient. For joint replacement and time on DMARDs, Weibull distributions were used. A random variable  $X$  has a Weibull distribution with shape parameter  $a$  and scale parameter  $b$  if  $\left(\frac{X}{b}\right)^a$  has an exponential distribution with unit mean. Thus, the Weibull distribution is strictly more general than the constant-risk exponential distribution in that it reduces to the exponential distribution when  $a = 1$ . If  $a < 1$ , the risk decreases over time, while if  $a > 1$ , the risk increases over time.

### Sampling from conditional distributions

When sampling times to events, it is necessary to sample from conditional survival distributions allowing for current age or time spent 'at risk'. Details are shown in Appendix 5.

## Data used in the BRAM

### Patient and DMARD characteristics

Table 4 shows the age and gender distribution used in the model. This was calculated by comparing incidence data from Symmons and colleagues<sup>11</sup> with estimates of the total population at risk.

The initial distribution of HAQ scores shown in Table 5 was based on data from Wiles and colleagues.<sup>12</sup>

Thus, averages were taken across age and gender subgroups, and across the initial HAQ score

**TABLE 5** Distribution of initial HAQ scores<sup>12</sup>

HAQ	0.25	0.75	1.5
Percentage	25	50	25

subgroups. This is driven by data limitations. The model could be used to analyse subgroups independently, if reliable data were available.

For the time to joint replacement, a Weibull distribution was used with parameters  $a = 1.4$ ,  $b = 56.2$  for initial joint replacement, and  $a = 0.43$ ,  $b = 16.3$  for subsequent replacements. This was obtained by fitting curves to data from Wolfe and Zwillich.<sup>13</sup> Data were used from the same paper to estimate their dependence on HAQ.

The reduction in HAQ score when starting a new DMARD is shown in Table 6. Figures come from the source referenced, with numbers converted to the nearest multiple of 0.125 as this is the smallest unit of change on the HAQ score. For the DMARDs not referenced, the assumption that they are the same as sulfasalazine has been sustained from the BPM. Further details about the sources of data about HAQ improvements on different DMARDs can be found in Appendix 6.

The length of time, pattern and source of data used to estimate the amount of time a patient will spend on a DMARD are given in Table 7.

For all patients with RA, it was assumed that the average time interval to see a 0.125 increase in HAQ score was 4.0 years. This is based on data reported by Scott and colleagues,<sup>26</sup> which indicates a rate of change in HAQ of 0.031 per annum.

### Cost data

Costs are incurred in the model for the use of treatment and for joint replacement. The cost of treatment includes monitoring as well as drug costs (Table 8). All DMARDs require relatively intensive monitoring in early use, reducing to a steady-state monitoring arrangement particular to the DMARD in question. As in the BPM,<sup>2</sup> these have been treated as a start-up cost, which is assumed to occur at the instant of starting the DMARD, followed by a steady-state cost per year

**TABLE 6** HAQ improvements from starting each DMARD

DMARD	AZA	CyA	Etan <sup>14-16</sup>	GST	HCQ	Infl <sup>a</sup>	LEF <sup>17,18</sup>	MTX <sup>18</sup>	D-Pen	SSZ <sup>17</sup>	Comb
	0.25	0.25	0.625	0.25	0.25	0.625	0.5	0.375	0.25	0.25	0.25

Etan, etanercept; Infl: infliximab.  
<sup>a</sup> Quartey P (Schering-Plough Ltd: personal communication, 2001).

**TABLE 7** Distribution of time on each DMARD

DMARD	Shape	Scale	Source
Sulfasalazine	0.71	2.76	Maetzel <i>et al.</i> <sup>19</sup>
Methotrexate	0.77	4.62	Maetzel <i>et al.</i> <sup>19</sup>
Etanercept	1.52	4.72	Crnkic <i>et al.</i> <sup>20</sup>
Infliximab	1.29	2.66	Crnkic <i>et al.</i> <sup>20</sup>
Gold	0.71	3.08	Maetzel <i>et al.</i> <sup>19</sup>
Azathioprine	0.73	1.60	Hawley and Wolfe <sup>21</sup>
Penicillamine	0.62	1.86	Pincus <i>et al.</i> <sup>22</sup>
Hydroxychloroquine	1	3.62	Maetzel <i>et al.</i> <sup>19</sup>
Leflunomide	0.67	3.10	Crnkic <i>et al.</i> <sup>20</sup>
Ciclosporin	1	1.70	Lynch and Robinson <sup>23</sup>
Combination	1	1.74	Tugwell <i>et al.</i> <sup>24</sup> Gerards <i>et al.</i> <sup>25</sup>

**TABLE 8** Assumptions concerning patient monitoring

DMARD	Pretreatment	On treatment
Infliximab	FBC, ESR, CRP, LFTs, anti-nuclear antibodies, anti-DNA antibodies, CXR	FBC, ESR, CRP, U&E, LFTs at weeks 2, 6 and every 8 weeks (at times of infusions). Anti-nuclear antibodies and anti-DNA antibodies may be done twice a year
Etanercept	FBC, U&E, ESR and/or CRP, LFTs, CXR	FBC, ESR, CRP, U&E, LFTs, at weeks 2, 4, 8 and 12, then every 8–12 weeks thereafter
Sulfasalazine	FBC, ESR and/or CRP, LFTs	FBC every 2 weeks for first 12 weeks. LFTs every 4 weeks for first 12 weeks. FBC and LFTs every 3 months thereafter
Methotrexate	FBC, U&E, ESR and/or CRP, LFTs and CXR	FBC, LFTs (± U&E) every 2 weeks while dose changes being made (i.e. for between 4 and 6 months). Once stable, FBC, LFTs (± U&E) monthly
Gold (myocrisin)	FBC, U&E, ESR and/or CRP, LFTs, urinalysis	FBC, U&E, LFTs, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, and then monthly. Treatment given by i.m. injections
Hydroxychloroquine	No specific monitoring requirements. Assumption: routine blood checks to monitor disease state (i.e. FBC, ESR or CRP, U&E, and LFTs)	
Penicillamine	FBC, U&E, ESR and/or CRP, LFTs, urinalysis	FBC, U&E, ESR or CRP, urinalysis every 2 weeks until stable dose (assumed to be 4 months). Every month thereafter
Leflunomide <sup>a</sup>	FBC, U&E, ESR and/or CRP, LFTs, BP, urinalysis	FBC every 2 weeks for 6 months, every 8 weeks thereafter. BP every 2 weeks for 3 months. LFTs monthly for 6 months, every 8 weeks thereafter
Ciclosporin	FBC, U&E (× 2), blood lipids, ESR and/or CRP, LFTs, urinalysis, normal BP (× 2)	FBC, U&E, BP every 2 weeks until stable dose for 3 months. The latter guidance is unlikely to be adhered to in practice, so it was assumed that checks would be done every 2 weeks for 4 months. LFTs monthly and serum lipids every 6 months
Azathioprine	FBC, U&E, ESR and or CRP, LFTs	FBC and LFTs weekly for 6 weeks, then every 2 weeks for 3 visits. Monthly thereafter

<sup>a</sup> BSR guidelines not available, monitoring requirements estimated. FBC, full blood count; ESR, erythrocyte sedimentation rate (not strictly required for monitoring drugs, but will usually be done to monitor disease activity; it was assumed that it is done on each occasion); CRP, C-reactive protein; LFTs, liver function tests; CXRs, chest X-ray; U&E, urea, electrolytes and creatinine; urinalysis, urine dipstick test for blood, protein and glucose; BP, blood pressure.



TABLE 9 Unit costs

Resource item	Unit cost (£)	Assumptions	Source for unit costs
<b>Visits</b>			
GP (per visit)	18.00		Netten <i>et al.</i> (2000) <sup>27</sup>
Hospital outpatient (per visit)	78.00		
Hospital inpatient (per day)	202.00		
<b>DMARDs<sup>a</sup></b>			
Sulfasalazine	48.65	2.5 g/day	British National Formulary
Methotrexate	10.21	15 mg/week, orally	
Gold	82.08		
Hydroxychloroquine	45.51	300 mg/day	
Penicillamine	29.88	500 mg/day	
Leflunomide	139.50	20 mg per day	
Ciclosporin	520.06	3.25 mg/kg per day, 70 kg patient	
Azathioprine	47.11	150 mg/day	
Infliximab	2216.40	70 kg patient, drug wastage if full vials not used, cost per administration of £124	
Etanercept	2072.00	102 doses per annum	
<b>Tests</b>			
FBC	11.15		Trust finance department <sup>b</sup>
ESR	11.15		
LFT	6.19		
U&E	6.19		
CXR	20.00		
Urinalysis	0.08		
<sup>a</sup> Drug costs for 3 months, including administration costs.			
<sup>b</sup> Source: University Hospital Birmingham NHS Trust. Price year: 2000.			

on the DMARD. For palliation, there is no start-up cost, but there is a steady-state cost per year.

Details of the unit cost data used in this analysis are shown in *Table 9*.

Joint replacement is treated as an event in the model since the time taken is negligible compared with time spent on DMARDs. A one-off cost is applied at the time of the joint replacement. In the absence of reliable data, this was estimated at £5000, to be varied in sensitivity analysis.

### Toxicity

In the model toxicity was explicitly modelled for methotrexate and ciclosporin only, because these are the components of combination therapy which could not be used if either of these had been quit on grounds of toxicity. For ciclosporin it was assumed drug cessation was due to toxicity with a probability of 0.8 regardless of the time spent on the drug.<sup>23</sup> For methotrexate, the probability  $p$  was set to depend on the time  $t$  years on the drug, by the formula

$$p = 0.362 + 0.115e^{-0.457t}$$

which was derived from a comparison between the survival curves given by Maetzel and colleagues.<sup>19</sup>

## QoL and mortality

### HAQ score

The HAQ is by far the most common disability assessment questionnaire used in studies of RA. It is scored from 0 to 3, where a score of 0 is normal health and 3 the worst disability. Fuller details on the scoring algorithm are given in Appendix 7. The patient's initial HAQ score in the model is drawn from an appropriate distribution. It is assumed that starting a DMARD has a positive effect and so HAQ is reduced. Similarly, if the DMARD has to be quit there is assumed to be an increase in HAQ. Within the model, HAQ is also reduced at successful joint replacement. The general decline in a patient's condition that tends to occur over time is modelled by stepped HAQ increases.

### QoL calculations

Benefits in the model are measured in QALYs. These are calculated as the area under a curve plotting a QoL score against time in years.

Therefore, it is necessary to estimate the relationship between HAQ and various model parameters: QoL, mortality and joint replacement.

### **Relationship between HAQ and utility**

It is beyond the scope of this report to provide a detailed appraisal of disability and QoL measures in RA. This section describes briefly the relationship between the HAQ and health utility as it pertains to this economic model. For utility, the focus is on EuroQol EQ-5D, a widely used validated health profile and utility measure, rather than other commonly used health questionnaires such as the Short Form 36 (SF-36). This is done because of the difficulties associated with calculating health utility from other measures. Moreover, the SF-36 is known to have ceiling and floor effects in patients with RA (in functional classes I and IV; see Appendix 8), further limiting its usefulness.<sup>28</sup> Unfortunately, the EuroQol has not been evaluated in long-term studies of RA populations, but data on HAQ are available over several decades. These limitations determined several aspects of the economic model and key data inputs in the model rely heavily on HAQ, notwithstanding some concerns with HAQ, as described below.

The EQ-5D has two parts. One assesses self-reported problems in areas of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each may be scored at three possible levels of severity, designated 'no problem', 'some problem' and 'extreme problem'. This yields a possible 243 combinations of health states. The second part of EQ-5D records self-assessed general health on a vertical line scored from 0 to 100, with 0 corresponding to worst imaginable health and 100 to best imaginable health. Both parts of EQ-5D have been validated in RA and shown to correlate with measures of disease activity in RA and to be responsive to change in disease status over 3 months.<sup>29,30</sup> However, Wolfe and Hawley reported that the scoring properties of EuroQol pose problems in patients with rheumatic diseases.<sup>31</sup>

The term 'disability' in the context of HAQ refers to difficulty in carrying out a task and not the broader concepts of disability embraced by the World Health Organization.<sup>32,33</sup> HAQ is a 20-item self-report questionnaire that asks about functional limitations in respect of dressing and grooming, arising (out of a chair or bed), eating, walking, hygiene, reaching, gripping and other activities. A minimum score of 0 and a maximum score of 3 are possible, with increments of 0.125 units.<sup>33</sup> The scale, however, is quasi-dimensional and changes

in HAQ between 1 and 2 are of less clinical relevance than those between 0 and 1.<sup>34</sup>

Although clinical experience shows that physical disability in RA increases with time, it is also true that patients presenting for medical care, or at disease onset, have significant self-reported disability (HAQ score around 1.0). Clearly, one of the goals of medical care is to improve this functional limitation. Pain is the strongest determinant of HAQ disability (correlation coefficient 0.634), closely followed by depression (correlation coefficient 0.491), although mood is not assessed within HAQ. Disease duration and ESR (a marker of disease activity) are less important (coefficients of 0.227 and 0.319, respectively) determinants of HAQ, despite ESR being a strong predictor of structural damage.

HAQ scores for individual patients can be extremely labile especially during the early years of disease.<sup>12</sup> This may be because early in disease HAQ reflects joint inflammation that may be reversible with effective treatment, whereas later in disease HAQ reflects joint damage that is more likely to be irreversible. However, Wolfe, in exploring the course of HAQ in individual patients, found that many patients have a chaotic unpredictable course while others show an initial improvement and a decline with time.<sup>35</sup> He says that, "duration of disease is only weakly related to HAQ score and that current disease activity, pain, and psychological factors have far more to do with HAQ score than the persistence of disease over time". He noted that disease duration could only explain 5% of the variance in individual HAQ scores. Scores tend to be worse in women at any one time and the rate of decline with time was also greater in women.<sup>35</sup> Wolfe noted that, taken over many years, HAQ disability increases very slowly over time (0.03 units per year; it is suggested that a clinically meaningful change in HAQ is 0.25 units<sup>36</sup>). A study from Newcastle upon Tyne also showed an identical annual decline in HAQ.<sup>37</sup> Whether all such change can be attributed to disease, or to ageing, is unclear. A cross-sectional study of HAQ, in RA and the general population, showed that HAQ scores differed from 0.6 at 40–49 years to 1.11 in those over 70 years with RA, and from 0.01 to 0.74 in the background population.<sup>38</sup>

A few studies have measured HAQ and EQ-5D in the same population of RA patients and have looked at their relationship.<sup>29–31,39</sup> Perfect correlation between these two measures cannot be expected as their goals are to measure different,

albeit related, aspects of health. For example, gastrointestinal symptoms, which would not be expected to influence HAQ scores, have an impact on EQ-5D utility scores in RA patients.<sup>40</sup> Nevertheless, there is at least moderate correlation between HAQ and EQ-5D ( $r$  values in the range 0.42 to 0.78).

The researchers were supplied with the data set reported by Hurst and colleagues.<sup>30</sup> Using the EQ-5D 'social tariff' for the QoL variable, the equation  $QoL = 0.862 - 0.327 HAQ$  fits the data with an  $R^2$  value of 0.539. Clearly, general health-related QoL includes dimensions that are not reflected in the HAQ score. However, the regression equation used allows one to make a reasonable estimate of the QALY difference between two strategies. The method of modelling HAQ changes means that the HAQ score is constant between events in the model. Thus, one can assume a constant QoL score over the periods between events. For starting and quitting DMARDs, it is assumed that there is a gradual improvement and decline; these are modelled as one-off deductions from the total QALYs. Further details on the regression analysis of QoL against HAQ are given in Appendix 9.

#### **Relationship between HAQ and mortality**

A diagnosis of RA is associated with an increased risk of dying early. The extent of this hazard varies because of differences in RA populations (e.g. a clinic setting versus a community setting) and in RA diagnostic criteria among reported studies. A recent report of community-recruited patients in the UK did not find an increased mortality in patients with 'inflammatory polyarthritis' or those fulfilling the 1987 ACR criteria for RA.<sup>41</sup> However, patients with rheumatoid factor (RF) in a blood test had an increased all-cause mortality [standardised mortality ratio (SMR) males 1.51, CI 1.06 to 2.08; females 1.41, CI 0.93 to 2.05]. Predominantly clinic populations, from US centres, showed that the SMR in RA was 2.26 and that it increased with greater duration of disease.<sup>42</sup> Mortality in RA is also related to the degree of disability such that mortality was increased by 1.77 for each increase in HAQ score.<sup>43</sup> The relationship between disability and mortality has been used to estimate the costs of RA.<sup>44</sup> This relationship perhaps accounts for the association of disease duration and mortality, since disability increases with disease duration. A recent meta-analysis found that the pooled mean SMR in RA was 1.7, indicating that mortality rate in RA was 70% greater than the general population.<sup>45</sup> However, the majority of these studies were not inception

cohorts; analysis of inception cohorts shows that the SMR was 1.22. This study also showed that the mortality of RA has not altered in more recent patient cohorts, suggesting that modern treatments have not had an impact on mortality in RA. However, it has been suggested recently that methotrexate may reduce mortality in RA (mortality hazard ratio 0.4 compared with no methotrexate use).<sup>46</sup>

Factors associated with increased mortality have been examined in relatively few studies. Wolfe and colleagues sought predictors of mortality at three US centres. Age and male gender were associated with early mortality at all three centres. Disability, measured as HAQ score at one centre, was also linked with early mortality [relative risk (RR) 1.33/unit; CI 1.099 to 1.61].<sup>42</sup> Certain disease markers, such as ESR and the presence of RF in blood or rheumatoid nodules, led to a greater risk of death. The diagnosis of RA was based on the 1958 criteria for RA (definite or classic)<sup>47</sup> or the 1987 criteria.<sup>41</sup> This requirement is likely to exclude a proportion of patients treated as RA in clinical practice, since criteria for RA tend to be acquired with time.<sup>48</sup> Wolfe and colleagues acknowledge that, as with many studies of mortality in RA, their patient population did not consist of an inception cohort.<sup>42</sup>

In the present base-case analysis a mortality ratio of  $1.33^{HAQ}$  was used. Full discussion of this is presented in Appendix 4.

#### **Joint replacement in RA and relationship between HAQ and joint replacement**

The need for joint replacement surgery in patients with RA is widely perceived to reflect a failure of medical therapy; that is, joint damage and failure is directly a result of inadequate disease control. This view presupposes that all joint failure needing replacement surgery is due entirely to the RA disease process. Although it is true that destruction of large joints warranting replacement occurs commonly in RA, it is also true that coexisting osteoarthritis is also common and could account for a substantial proportion of joint replacement surgery in RA patients. For example, cross-sectional studies of the general population requirement of hip and knee replacement surgery for osteoarthritis is estimated at 2.2 (CI 1.6 to 2.9) and 20 (CI 18 to 23, people aged 55 years and more) per 1000 population, respectively.<sup>49,50</sup> Thus, attributing all large joint replacement surgery to the RA disease process in RA patients is inaccurate.

Little is known about the proportions of patients with RA who need joint replacement and nothing is known about the potential impact of DMARDs on preventing joint replacement surgery. A US study, using a database of 1600 RA patients, found that 25% of patients have total joint arthroplasty within 22 years of disease onset, primarily knee (57%) and hip (34%) joints. Fifty per cent of those who have had one joint replaced will have another replaced within 7 years.<sup>13</sup> Measures of disease activity and severity such as ESR, disability and radiographic erosions predicted joint replacement. Disability was assessed with HAQ scores. Scores were grouped 0–1, 1–2 and 2–3, and data are presented as time-to-event curves. These show that approximately 25% of the most disabled patients had an arthroplasty by 8 years compared with fewer than 10% of the least disabled. Wolfe and Zwillich also report data on the rate of failure of a primary joint replacement.<sup>13</sup> A second artificial joint was placed at the site of a previous replacement in 6% (CI 4 to 10%) of knees within 10 years and 4% of hips (CI 2 to 11%). Surgery other than another new joint at the same site was also done in 6% of knees within 10 years and 9% of hips.

Major joint replacement surgery (total hip, knee, shoulder and elbow replacements), in a UK cohort, occurred in 7.6% of patients (55 patients) by 5 years.<sup>51</sup> Older patients and those with worse initial HAQ scores were more likely to need surgery, but odds ratios were not given. By contrast, the proportion of patients having joint replacement in a Swedish cohort was 14% (nine patients) after 5 years.<sup>52</sup>

Radiographic damage in the small joints of hands and feet is used as a key outcome measure in therapeutic trials in RA. Small joint damage is known to correlate with large joint damage, but it is also known that there is considerable variation in joint damage at different anatomical sites.<sup>26,53</sup> The relationship between small joint damage and the propensity for joint replacement surgery is unknown. In view of this the model focused on disability as a determinant of joint replacement, rather than scores of small joint damage. This is justified by the lack of correlation between radiographic damage and direct medical costs,<sup>54</sup> in contrast to the correlation between costs and disability.<sup>55</sup>

Little published evidence was found on the relationship between HAQ and joint replacement (see Appendix 10 for details of a rapid review on this topic that did not cite HAQ data). Therefore,

the arbitrary assumption was made that joint replacement halved the HAQ score for a patient, to be tested in sensitivity analysis.

## Details of event and activity handling

### Initialisation

Each new virtual patient is assigned age, gender and starting HAQ score from the appropriate distributions. The number of DMARDs left and the identity of the first DMARD are determined according to the strategy currently being applied. Total costs and QALYs are set to zero, and the risk of joint replacement is set appropriately. The patient then moves to the event 'Start new treatment'.

### Start new treatment

This event can be reached either from 'Initialisation' or from 'Select next treatment'. Two issues are handled in this event. First is the question of the time the patient will spend on the DMARD. The time to be spent on the DMARD is sampled from the Weibull distribution with parameters appropriate to the particular DMARD. This is added to the patient's current age to give the age at which the DMARD will be quit. Using age in this way avoids the need to resample after HAQ changes or joint replacement. In the case of palliation, the age to quit is set at 200: since the life tables used end at the age of 101, quitting palliation cannot occur.

The other issue handled in this event is the question of start-up costs and utility loss. If this treatment is the first after the divergence point between strategies, total costs and QALYs are set to the start-up costs and QALY losses appropriate for that treatment (zero for palliation), and the fact that the divergence point has been reached is recorded. Otherwise, start-up costs and QALY losses are added to the current totals. The patient then moves to the activity 'On treatment'.

### On treatment

The time to quitting the treatment is found by subtracting the patient's current age from the age at which the treatment is to be quit. Times to death, HAQ increase and joint replacement are sampled from appropriate distributions. Each of the times sampled is calculated on the assumption that no other event occurs first. Therefore, whichever of the four times is the lowest represents the event that actually occurs next. If the patient's current HAQ score is 3, then the time

to HAQ increase is set to 200 years, so that HAQ increase will not occur. If joint replacement is not allowed, then time to joint replacement is set to 200 years. Note that for a patient on palliation with HAQ score of 3, the only remaining event is death.

Once the time to the next event has been determined, total costs and QALYs are increased to allow for the steady-state time spent on the treatment. If the next event is a change in HAQ score, then HAQ is increased by 0.125 and the patient returns to the state 'On treatment'. Otherwise, the patient moves to 'Death', 'Joint replacement' or 'Quit DMARD', as appropriate.

#### HAQ increase

This is not modelled as a separate event, but included at the end of the activity 'On treatment'.

#### Quit DMARD

Utility is adjusted for end effects. In the case of CyA or MTX, it is determined whether the reason for quitting is toxicity. In any case, the next event is 'Select next treatment'.

#### Select next treatment

If there are no DMARDs left, the next treatment is palliation. If the next DMARD in the sequence is a single DMARD, this DMARD is selected. If the next DMARD is combination therapy, the next treatment depends on whether one of CyA or MTX was quit for reasons of toxicity. If so, combination therapy is not used and no treatment on the list is selected in this event. If combination therapy can be used, it is selected. If combination therapy has been discarded, and therefore no treatment has been selected at this event, the next event is repeating 'Select next treatment'. In all other cases, the next event is 'Start new treatment'.

#### Joint replacement

There is a small probability of death at joint replacement. Otherwise, the replacement may succeed or fail. A failed joint replacement may be repeated or accepted. In case of a repeat, the patient returns to 'Joint replacement'. Otherwise, the patient moves to 'On treatment'.

#### Death

If the patient has not reached the divergence point between strategies, the patient's history is not counted towards the sample totals. A new patient is then initialised. Otherwise, the total costs and QALYs are counted towards the simulation mean and standard deviation.

## Validation comparison of BRAM and BPM

As part of the validation process for the BRAM, its results were compared with the results produced by the BPM reported by Jobanputra and colleagues.<sup>2</sup> The BRAM was set to exclude joint replacements and run using the same parameters as the BPM. This involved changing the mortality to a standard hazard ratio of 1.5 regardless of HAQ score, and the conversion from HAQ gain to QoL loss to 0.2. The strategies compared are shown in *Table 10* and the results are shown in *Table 11*.

The BPM ran for 10,000 (virtual) patients in each of three strategies. The way in which the BPM ran allowed the output to be treated as paired data and thus minimised the sampling variance of the difference between the results of the strategies. The structuring of the BRAM to allow for effects of DMARDs on mortality and joint replacements meant that this was no longer possible. Treating the output from running the model under

**TABLE 10** Strategies used in the BPM

Strategy	Base	Etanercept	Infliximab
<b>Common DMARDs before divergence of treatment sequence</b>	Sulfasalazine Methotrexate	Sulfasalazine Methotrexate	Sulfasalazine Methotrexate
<b>DMARD sequence after divergence of treatments</b>	Gold Azathioprine Penicillamine Hydroxychloroquine Leflunomide Ciclosporin MTX/CyA Palliation	Etanercept Gold Azathioprine Penicillamine Hydroxychloroquine Leflunomide Ciclosporin MTX/CyA Palliation	Infliximab Gold Azathioprine Penicillamine Hydroxychloroquine Leflunomide Ciclosporin MTX/CyA Palliation

**TABLE 11** Comparison of BRAM results with BPM results

(a) BRAM simulation results (1,000,000 virtual patients in each arm)							
Strategy	% Ending on palliation	Cost/patient (£)		QALYs/patient			
		Mean	q.s.e.	Mean	q.s.e.		
Etanercept	45.6	40,717	17.46	10.731	0.0062		
Infliximab	49.4	34,617	14.46	10.611	0.0062		
Base	54.9	15,846	5.31	10.456	0.0061		
(b) BRAM ICER calculations							
Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	24,871	18.25	0.276	0.0087	90,226	84,853	96,326
Infliximab – base	18,771	15.41	0.155	0.0087	120,882	108,695	136,148
Etanercept – infliximab	6100	22.67	0.120	0.0087	50,678	44,239	59,311
Corresponding results from BPM (10,000 virtual patients in each arm)							
Etanercept – base					83,095	80,863	85,454
Infliximab – base					115,397	111,822	119,209
Etanercept – infliximab					44,912	43,797	46,084
q.s.e., quasi-standard error of the difference in means. This reflects only the uncertainty due to sampling within the model, not the parameter uncertainty. It can be reduced by increasing the number of virtual patients in the model and is quoted to show that a sufficient number has been used.							
Low/high: low and high ends of ~95% quasi-confidence intervals (reflecting only sampling uncertainty within the model).							

different strategies as unpaired data means that the variance of the difference has to be calculated as the sum of the variances for the individual strategies. These sampling variances in turn allow for the variation in lifetime and initial assumed QoL for the patients in the model. Thus, the quasi-confidence intervals in the BRAM are somewhat wider than those in the BPM, even though a much larger number of patients was used in the BRAM. A further difference between the BRAM and the BPM is that patients who did not

reach the divergence point were included in the BPM with zero differences. Such patients were excluded from the sampling in the BRAM; the model was run for the required number of patients, counting only those who reached the divergence point. By comparison with the BPM, the mean differences in costs and QALYs are higher, but the ICER should not be changed. The results shown in *Table 11* confirm that the BRAM has reproduced the results of the BPM to within sampling error.

# Chapter 4

## Results

### BRAM base-case results

Following the encouraging results from the validity comparison of the BRAM with the BPM (reported above), the BRAM was run with its default data set (as described in Chapter 3, Data used in the BRAM), initially for the three strategies shown in *Table 10*. Because of the uncertainties relating to available data on the effect of DMARDs on joint replacement and the effect of joint replacement on HAQ score, the initial running of the base-case BRAM did not consider the issue of joint replacement. The results are shown in *Table 12*. (For all runs of the BRAM reported here, the estimates of the mean cost and mean QALYs for each strategy are detailed in Appendix 11.)

The results of this initial running of the BRAM suggest incremental costs that are similar to those estimated for the validation comparison with the BPM (see *Table 11*). However, using improved data sources, the estimates of the incremental QALYs for each comparison are nearly double, with the consequence that the ICER values are almost halved. For example, the revised estimate of the cost–utility ratio for the use of etanercept in the DMARD sequence reported in *Table 10* is now estimated to be just over £50,000 per QALY, compared with the earlier estimate of just over £90,000 per QALY.

Given the methodological nature of this project, some assumptions were made relating to joint replacement, to allow BRAM results to be reported when issues of joint replacement are included. It must, however, be emphasised that the results reported below are illustrative only, given the uncertainties in the joint replacement estimates. These runs of the BRAM again used the three strategies shown in *Table 10*. The assumption is made that joint replacement leads to a halving of the HAQ score. In addition, the cost of a joint replacement is assumed to be £5000. The results for this run of the BRAM are reported in *Table 13*.

The results indicate that the incremental QALY scores are lower when joint replacement issues are included in the model, but that the cost estimates are virtually identical. The consequence is that the ICERs associated with the policy of using the new TNF inhibitors are higher when joint replacement is considered. The uncertainty in the cost of joint replacement was explored by varying the cost to an extreme value (i.e. £200). The results suggest that, overall, the ICER values are highly insensitive to the cost of joint replacement.

### Variation in comparators

One of the central issues that has been explored in this project is the importance of specifying the

**TABLE 12** Base-case results for the BRAM (without joint replacement)

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,283	18.03	0.501	0.0073	50,442	49,018	51,950
Infliximab – base	18,972	15.26	0.277	0.0073	68,591	65,172	72,390
Etanercept – infliximab	6,312	22.44	0.225	0.0073	28,096	26,377	30,054

**TABLE 13** Results including joint replacement at £5000 (assumption)

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,257	18.85	0.426	0.0082	59,289	57,102	61,651
Infliximab – base	18,957	16.15	0.232	0.0082	81,583	76,233	87,739
Etanercept – infliximab	6,300	23.14	0.194	0.0081	32,535	30,001	35,537

correct comparison in the analysis being undertaken. This has been investigated using two separate analyses: first, the situation of comparing the anti-TNFs with placebo, and second, the comparison of a sequence using anti-TNFs with a sequence that represents current practice in the UK, as reported in Chapter 2.

### Placebo comparisons

An important issue in the construction of both the BPM and the BRAM was the idea that for some patients, anti-TNFs would simply displace other DMARDs rather than give extra time on active treatment. A comparison against placebo, defined in terms of no displacement of other DMARDs, would not allow this issue to be explored and, therefore, would tend to exaggerate the benefits of anti-TNFs. To test the effect of this on the analysis results, the BRAM was run with its default data set (as described in Chapter 3) for the three strategies shown in Table 14. This is equivalent to a comparison against placebo. The results are shown in Table 15.

The ICERs shown in Table 15 when an inappropriate comparator of placebo is used are consistently lower than in the base case shown in Table 12 where appropriate comparator drugs are used. The focus of the BRAM on a drug sequence helps to avoid the incremental cost-effectiveness values of new treatments appearing lower than they really are when inappropriate comparators are used.

### Model run with current UK practice on DMARD use

As reported in Chapter 2, to ensure that the model truly reflects modern clinical practice in the UK, a systematic review of DMARD use in the

treatment of RA and a survey of current practice by rheumatologists in the UK were undertaken for this report.

The intention was to test the effect on the analysis results of using the DMARD sequence that represents current UK practice. Therefore, the BRAM was run with its default data set (as described in Chapter 3, Data used in the BRAM) for the strategies shown in Table 16. The results are shown in Tables 17–20.

Based on the survey reported in Chapter 2, the sequences of DMARDs other than anti-TNFs to consider are shown in Table 16.

Each of these strategies was considered in turn, using each anti-TNF as possible third line therapy. The results are shown in Tables 17 and 18. They are not much different from the base-case results.

The results of the survey also allowed consideration of the point where anti-TNF was most likely to be used. For each of the strategies shown in Table 16, the likely point of use of an anti-TNF was immediately after leflunomide, that is in fourth place for strategy 1 and in sixth place for strategy 2. Each of these possibilities was tried in turn, with the results shown in Tables 19 and 20. These show more favourable results than the corresponding tables for use as third line therapy.

### Flexibility of the BRAM

As with any health technology assessment exercise, there remain some potentially important

**TABLE 14** Strategies for comparison of anti-TNFs versus placebo

Strategy	Base	Etanercept	Infliximab
<b>Common DMARDs before divergence of treatment sequence</b>	Sulfasalazine Methotrexate	Sulfasalazine Methotrexate	Sulfasalazine Methotrexate
<b>DMARD sequence after divergence of treatments</b>	Palliation	Etanercept Palliation	Infliximab Palliation

**TABLE 15** Results for comparison of anti-TNFs versus placebo

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	29,066	17.59	0.687	0.0068	42,289	41,464	43,148
Infliximab – base	21,330	14.39	0.381	0.0068	55,988	54,053	58,067
Etanercept – infliximab	7,736	22.64	0.306	0.0068	25,252	24,168	26,439



**TABLE 16** Strategies to be considered as a result of our survey

	Strategy 1	Strategy 2
Sequence of DMARDs used	Sulfasalazine Methotrexate (MTX) Leflunomide Gold (GST) Azathioprine Ciclosporin (CyA) Combination MTX + CyA	Sulfasalazine Methotrexate (MTX) Hydroxychloroquine Gold (GST) Leflunomide Azathioprine Ciclosporin (CyA) Combination MTX + CyA

**TABLE 17** Results for comparison using new strategy 1

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,663	18.11	0.555	0.0071	46,277	45,121	47,495
Infliximab – base	19,213	15.34	0.309	0.0071	62,223	59,497	65,211
Etanercept – infliximab	6,451	22.53	0.246	0.0071	26,245	24,798	27,871

**TABLE 18** Results for comparison using new strategy 2

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,994	18.28	0.515	0.0072	50,513	49,133	51,972
Infliximab – base	19,397	15.54	0.283	0.0072	68,508	65,193	72,177
Etanercept – infliximab	6,597	22.66	0.231	0.0072	28,501	26,817	30,412

**TABLE 19** Results for comparison using new strategy 1 with anti-TNFs in fourth place

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,561	18.10	0.626	0.0067	40,863	40,004	41,760
Infliximab – base	19,180	15.26	0.349	0.0067	54,914	52,890	57,100
Etanercept – infliximab	6,381	22.57	0.276	0.0067	23,098	22,016	24,292

**TABLE 20** Results for comparison using new strategy 2 with anti-TNFs in sixth place

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	26,240	18.04	0.663	0.0060	39,564	38,856	40,299
Infliximab – base	19,701	15.11	0.375	0.0060	52,574	50,942	54,313
Etanercept – infliximab	6,539	22.63	0.289	0.0061	22,666	21,741	23,673

**TABLE 21** Results with minimum improvement for joint replacement

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,225	18.95	0.482	0.0075	52,304	50,721	53,989
Infliximab – base	18,946	16.27	0.261	0.0075	72,479	68,543	76,894
Etanercept – infliximab	6,279	23.23	0.221	0.0075	28,427	26,604	30,519

**TABLE 22** Results with maximum improvement in HAQ to zero

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,287	18.81	0.391	0.0091	64,666	61,796	67,815
Infliximab – base	18,961	16.07	0.217	0.0091	87,529	80,755	95,543
Etanercept – infliximab	6,326	23.10	0.174	0.0091	36,270	32,851	40,483

**TABLE 23** Results for the BRAM including offset costs

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	24,303	22.56	0.501	0.0073	48,487	47,117	49,938
Infliximab – base	18,351	20.22	0.277	0.0073	66,349	63,040	70,025
Etanercept – infliximab	5,952	26.30	0.225	0.0073	26,494	24,869	28,347

uncertainties in this evaluation work. A major benefit associated with the adoption of a modelling approach is that the importance of some of the uncertainties can readily be explored. The BRAM was used to demonstrate how the sensitivity of the analysis results to variation in key assumptions and data-based estimates can be explored.

### Effect of joint replacement on HAQ

The base-case results assume a somewhat arbitrary effect that joint replacement halves the HAQ score. This was tested to extremes: first, that joint replacement merely reduces HAQ by 0.125 (*Table 21*), and second, that joint replacement reduces HAQ to 0 (full health) (*Table 22*).

Comparing *Tables 21* and *22* shows that the ICERs for the newer treatments are higher if there is a large gain (i.e. reduced HAQ) from joint replacement surgery. This is because there is relatively less QALY gain from preventing the need for joint replacement. The ICERs are, however, not highly sensitive to the HAQ changes attributed to joint replacement.

An alternative way of allowing for the effect of joint replacements is to include within the model a cost associated with the severity of the patient's condition. The original and revised models used by Wyeth for the appraisal of anti-TNFs each included an annual cost of £860 per unit HAQ score. That was applied here to give a cost ranging from 0 at HAQ 0 to £2580 at HAQ 3. Including these costs gives the results shown in *Table 23*. Compared with the base-case results in *Table 12*, the ICERs are slightly lower.

### Varying the assumptions concerning rate of change in HAQ

To test the assumption that HAQ change is slower for anti-TNFs than for DMARDs, further model runs were carried out, again using the strategies listed in *Table 10*. For these runs the average time to HAQ increase was set to 8 years for etanercept and infliximab, keeping all other DMARDs at 4 years. The results are shown in *Table 24*.

These results show that if the TNF inhibitors were shown to have a sustained impact on HAQ reduction in the longer term, their incremental

**TABLE 24** Results assuming that only anti-TNFs reduce the general deterioration in patient condition

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,338	18.06	0.841	0.0074	30,141	29,619	30,681
Infliximab – base	19,008	15.27	0.480	0.0073	39,566	38,395	40,811
Etanercept – infliximab	6,330	22.47	0.360	0.0075	17,571	16,863	18,341

**TABLE 25** Results assuming that all DMARDs reduce the general deterioration in patient condition

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	25,353	18.04	0.624	0.0083	40,601	39,554	41,705
Infliximab – base	19,018	15.27	0.348	0.0082	54,718	52,247	57,434
Etanercept – infliximab	6,335	22.45	0.277	0.0083	22,880	21,578	24,351

**TABLE 26** Results for a starting population of 15–25-year-old females

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	27,611	16.53	0.599	0.0088	30,141	29,619	30,681
Infliximab – base	20,158	14.04	0.315	0.0088	39,566	38,395	40,811
Etanercept – infliximab	7,454	21.07	0.284	0.0088	17,571	16,863	18,341

**TABLE 27** Results for a starting population of 75–85-year-old males

Comparison	Cost/patient (£)		QALYs/patient		ICER (£/QALY)		
	Mean	q.s.e.	Mean	q.s.e.	ICER	Low	High
Etanercept – base	17,147	15.76	0.331	0.0034	51,746	50,707	52,828
Infliximab – base	14,686	13.41	0.199	0.0033	73,950	71,542	76,526
Etanercept – infliximab	2,461	19.94	0.133	0.0034	18,535	17,591	19,585

cost-effectiveness would be reduced and they would represent better value for money.

To test the possibility that HAQ change is the same for all DMARDs, the average time to HAQ increase was set to 8 years for all DMARDs, keeping only palliation at 4 years. The results are shown in *Table 25*.

### Varying the proportions of patients who reach palliation

In the base case, approximately half of the patients complete the cycle of DMARDs and reach palliation. To see the effect that a change in this proportion has on the cost-effectiveness of anti-

TNFs, the model was rerun with different starting populations. The strategies used in these runs were again those listed in *Table 10*.

The results expected to be most favourable to anti-TNFs are those with a patient group with the longest life expectancy. The model was run with a starting population of females aged between 15 and 25 years. The results are shown in *Table 26*.

The run expected to be least favourable to anti-TNFs used a starting population of males aged between 75 and 85 years (the shortest survival times). The results are shown in *Table 27*.



# Chapter 5

## Discussion

### Main findings and generalisability of approach

This report has highlighted the problems inherent in economic evaluations when using trial-based effectiveness data where the comparator does not reflect current clinical practice. The work reported here indicates two important issues:

- that such data may give a misleading impression of the incremental cost-effectiveness of the new technology in question, and
- that this is likely to be a particular problem for treatments for chronic diseases, where the clinical pathway is often complex and for which appropriate comparative data tends to be limited.

The focus for this report was the evaluation of two new drugs, etanercept and infliximab, for use in the treatment of RA. The comparators in the trials of anti-TNFs tend to be placebo and so do not reflect clinical practice.

Earlier work by the authors showed that decision analytic models based on estimates of the effectiveness of the drug directly derived from the trial data were inadequate representations of real-life clinical practice and potentially resulted in misleading estimates of the incremental cost-effectiveness. In the case of the anti-TNFs, the ICERs resulting from the use of an inappropriate comparator of placebo were found to be consistently lower than in the case where appropriate comparator drug sequences were used. The focus of the BRAM on a drug sequence helps to avoid the incremental cost-effectiveness values of new treatments appearing lower than they really are when inappropriate comparators are used.

This report demonstrates ways of avoiding the use of inappropriate comparators through the use of suitably flexible modelling techniques. The aim was to restructure the RA model so that different sequences of treatment could be considered, and to determine the sequence that best represents current clinical practice in the UK. The main achievement of the work reported here was to bring about a more realistic modelling of real-life clinical pathways and events (i.e. a higher level of

descriptive validity for the RA model), as the model has developed from the BPM to the BRAM. This was brought about by overcoming structural and data limitations.

The modelling approach described here is potentially applicable to other conditions, especially chronic conditions that tend to be associated with a sequential approach to therapeutic options. An important issue that needs to be considered in applying this approach to other such chronic conditions is that data on current clinical practice are required. For many conditions such information is not routinely available. To ensure that the RA model reported here truly reflected modern clinical practice, a systematic review of drug use in the treatment of RA and a survey of current practice by rheumatologists in the UK were also undertaken.

It is important to consider the characteristics of the clinical application when deciding on the appropriate modelling approach. Like the BPM, the BRAM operates as an individual sampling model. This type of model is a form of discrete event simulation (DES) in which only one individual is considered at a time. The intention behind this type of model is to produce a realistic set of virtual patient histories, from which estimates of population mean costs and mean effects (e.g. QALYs) can be estimated. In principle, the richness of structure seen in the BRAM could have been achieved using a cohort model (e.g. a Markov model). However, from a practical point of view this would be highly problematic since it would require an enormous number of states to be defined and the model would be far slower to run than a DES model. The DES represents the most computationally efficient way of representing an adequate richness of structure. The suggestion might be made that a cohort model gives a more appropriate characterisation of uncertainty than a DES model. However, this is to ignore the many structural assumptions inherent in constructing a manageable cohort model. Therefore, DES should be preferred to cohort models whenever the 'real-life' system being modelled can be represented more efficiently using DES. This occurs whenever the number of potential patient pathways is so large compared with the number of patients that

an adequate cohort model would show the average number of patients as being far lower than 1 in the vast majority of states. Further discussion on the selection of an appropriate modelling approach in health technology assessment can be found in Karnon and Brown<sup>56</sup> and Barton and colleagues.<sup>57</sup>

## Strengths and limitations of the BRAM

An objective of the research reported here was to overcome some of the identified limitations of the BPM. Thus, the study sought to address the structural issues relating to mortality and QoL effects and to identify data on the general pattern of QoL of RA patients. The model has been successfully restructured so that different sequences of treatment can readily be considered, including the sequence that best represents current clinical practice in the UK. In addition, the flexibility inherent in using a modelling approach to consider these health policy questions has been demonstrated. One of the key uncertainties that can now be explored concerns the impact of new drugs on disease progression. Current evidence on this is weak but should new agents demonstrate a benefit of this sort then the BRAM would be a suitable vehicle through which to investigate the costs and full effects.

Inevitably, there remain problems and limitations with the BRAM, some of which are structural, but the vast majority of these are data limitations. For example, the economic evaluation currently takes an NHS perspective, with the consequence that the true cost savings associated with new effective DMARDs will be underestimated. This is because a considerable proportion of the cost of uncontrolled disease falls on patients and carers. Therefore, as data on this issue become available the BRAM provides a convenient tool through which the reanalysis might be undertaken. Several potentially important additional issues not currently considered by the BRAM are discussed below.

### Non-surgical hospitalisation for RA

Hospital admission for the treatment of RA or its complications, but not for surgery, varies greatly between UK centres.<sup>51</sup> A mean of 21% of patients were admitted at some time over 5 years, but differences between centres ranged from 4 to 42%. This difference is attributed to differences in the availability of inpatient beds for rheumatology. Few other studies have looked at the rates of

admission, and the authors are not aware of any studies that have looked at the determinants of hospital admission. This is unfortunate, since the largest proportion of health service costs incurred by RA patients is due to inpatient stays or day-case admissions (33%), while prescribed medication accounts for 30% of health service costs.<sup>58</sup> It is possible that effective disease control with more effective therapy could prevent hospital admission, but it is likely that psychosocial factors and co-morbidity, not just disease severity or complications, also accounts for hospital admission. In the absence of reliable data no allowance could be made for hospital admission in the model.

### Aids, appliances and home adaptations

Approximately 10% of the patients with RA require major adaptations or appliances, including stairlifts, major bathroom changes or regular use of wheelchairs. This proportion varies depending on the severity of the condition and on the patient's age. Such issues have not been considered in the analysis, largely because of data limitations.

### Compliance to DMARDs

A significant proportion of patients with RA do not comply with their medication at all or comply incompletely. For example, in a recent longitudinal study of RA patients in three European countries 24% of patients were consistently non-compliant with drug treatment (using a strict definition of compliance), 35% consistently compliant and 42% compliant at certain time-points.<sup>59</sup> Factors related to good compliance in this study were older age, female gender and satisfactory contacts with health professionals. Effective delivery of treatment can be ensured where a therapy is administered by health professionals, as with intramuscular gold or intravenous infliximab. This may improve the cost-effectiveness of such interventions despite the additional costs of health professional involvement. Although non-compliance may have a potentially negative impact on disease control it may also, in some cases, reduce drug toxicity not declared by patients and thereby enhance QoL. The potential impact of variable compliance was not considered in the model, for example as a result of different modes of administration. The authors are not aware of any data indicating differing rates of compliance between different DMARDs in RA populations. Nevertheless, allowing for non-compliance in the modelling seems to be warranted, not least because of the scale of this problem.

### **Reduced NSAIDs and corticosteroid requirement with good DMARD response**

A good response to any DMARD is likely to lead to reduced use of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics by RA patients. For example, 55% of patients decreased their dose of steroid, 25% ceased steroids and 6% increased their dose during treatment with etanercept.<sup>60</sup> Such changes in medication are likely to reduce health service costs not least because of medication costs, but potentially because of reduced toxicity from NSAIDs and corticosteroids. However, the authors are not aware of any data showing reduced steroid and NSAID complications as a result of effective DMARD use.

### **QoL and mortality**

The researchers tried to obtain the best available estimates for the parameters used in this model. However, evidence about the QoL pattern of a typical RA patient, how this is altered by each DMARD and the pattern of variation among individuals is limited. There is very limited evidence, if any, reliably relating American College of Rheumatology (ACR) responses to QoL.

However, this is a very common outcome measured in trials for new DMARDs. Because of this lack of data the BRAM uses HAQ score changes as a predictor of QALY scores. However, all studies, including those for the comparator drugs, have limited data on HAQ scores. Therefore, the model is based on crude estimates of the effect on HAQ of all treatments.

Although mortality benefits have been included in the model, these have been assumed to relate solely to HAQ scores.

### **Priorities for further research**

Studies are needed to investigate:

- the impact of DMARDs on QoL
- the impact of DMARDs on patient life expectancy
- variation in compliance rates across DMARDs
- costs associated with RA incurred by patients and their families, including fuller coverage of adverse events of DMARDs
- costs and benefits of other DMARD sequences (which could be explored using the BRAM).







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### Contributions of authors

Dr Pelham Barton was involved in the original design of the project. In addition, he led the design of the revised simulation model (Birmingham Rheumatoid Arthritis Model) and coded it in both TreeAge DATA Pro and Borland Delphi. He was responsible for running the model to produce all the results included in this report. He drafted the sections of the report relating to the structure of the model.

Dr Paresh Jobanputra helped to develop and analyse the survey of DMARD use in RA. He also researched clinical aspects of the model and contributed to the clinical parameters fed into the model, and read and commented on the draft the report.

Jayne Wilson did the searches, data extracted, analysed and wrote up results for the DMARD use systematic review. She also organised the practical side of the DMARD use survey, analysed the data and wrote up the results. She undertook a systematic search for information and analysed the findings for the background on joint replacements.

Professor Stirling Bryan was involved in the original design of the project. In addition, he contributed to the writing and editing of the report.

Dr Amanda Burls helped to develop the survey of DMARD use in RA and contributed to identifying

and finding empirical evidence to support the clinical parameters to feed into the model. She contributed to the writing and editing of the report.

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# Appendix I

## Search strategy for DMARD use systematic review

- |   |  |
|---|--|
| <p>1 Anti-Inflammatory Agents, Non-Steroidal/ or Antirheumatic Agents/ or Anti-Inflammatory Agents/ or Arthritis, Rheumatoid/ or Arthritis/ (91446)</p> <p>2 *Arthritis, Rheumatoid/th, dt [Therapy, Drug Therapy] (9282)</p> <p>3 Data Collection/ (45339)</p> <p>4 1 and 2 and 3 (14)</p> <p>5 Data Collection/ (45339)</p> <p>6 4 and 5 (14)</p> <p>7 Physician's Practice Patterns/ (11495)</p> <p>8 6 and 7 (5)</p> <p>9 2 and 7 (28)</p> <p>10 QUESTIONNAIRES/ (87157)</p> <p>11 1 and 2 (9282)</p> <p>12 3 and 10 (2202)</p> <p>13 11 and 12 and 7 (1)</p> <p>14 11 and 12 (2)</p> <p>15 AZATHIOPRINE/ (9624)</p> <p>16 limit 15 to human (8219)</p> <p>17 Chloroquine/ (8418)</p> <p>18 limit 17 to human (5474)</p> <p>19 Ciclosporine/ (13766)</p> <p>20 Ciclosporine/ (13766)</p> <p>21 limit 20 to human (9676)</p> <p>22 D-Penicillamine.mp. (3)</p> <p>23 limit 22 to human (3)</p> <p>24 Penicillamine/ or Arthritis, Rheumatoid/ or Antirheumatic Agents/ or Penicillins/ (72123)</p> <p>25 limit 24 to human (61901)</p> <p>26 Gold Sodium Thiomalate/ or Gold/ or Antirheumatic Agents, Gold/ (7412)</p> <p>27 limit 26 to human (4516)</p> | <p>28 gold.mp. or GOLD/ (28165)</p> <p>29 limit 28 to human (16961)</p> <p>30 Gold oral.mp. (8)</p> <p>31 limit 30 to human (8)</p> <p>32 HYDROXYCHLOROQUINE/ (912)</p> <p>33 limit 32 to human (858)</p> <p>34 HYDROXYCHLOROQUINE/ or Hydroxychloroquine.mp. (1141)</p> <p>35 limit 34 to human (1075)</p> <p>36 Leflunomide.mp. (396)</p> <p>37 limit 36 to human (212)</p> <p>38 METHOTREXATE/ (21037)</p> <p>39 limit 38 to human (17051)</p> <p>40 Methotrexate.mp. (25537)</p> <p>41 limit 40 to human (20807)</p> <p>42 Sulfasalazine/ (2572)</p> <p>43 limit 42 to human (2346)</p> <p>44 Sulfasalazine.mp. (2962)</p> <p>45 limit 44 to human (2705)</p> <p>46 16 and 18 and 19 and 21 and 23 and 25 and 27 and 29 and 31 and 33 and 35 and 37 and 39 and 41 and 43 and 45 (0)</p> <p>47 16 or 18 or 19 or 21 or 23 or 25 or 27 or 29 or 31 or 33 or 35 or 37 or 39 or 41 or 43 or 45 (121470)</p> <p>48 1 or 2 (91446)</p> <p>49 47 and 48 (47139)</p> <p>50 49 and 5 (42)</p> <p>51 49 and 7 (40)</p> <p>52 50 or 51 (76)</p> <p>53 50 and 7 (6)</p> <p>54 from 53 keep 1-6 (6)</p> |
|---|--|





## Appendix 2

### Summary of survey papers

**TABLE 28** Summary characteristics of reviewed papers

Study date	Authors	Country	Type of study	Patient type
1991	Kay and Pullar <sup>3,a</sup>	UK	Initial prescription; frequency of use	Initial therapy; generic patient
1992	Collins <i>et al.</i> <sup>9</sup>	USA	Vignette/DMARD of first choice	5 scenarios; increase in disease severity. Emphasis on methotrexate
1994	de Asit <i>et al.</i> <sup>7</sup>	France	Vignette/sequences sought	3 patients presented at year 0, year 1 and year 2, various outcomes assessed, e.g. increase/decrease in disease severity
1994	Conaghan <i>et al.</i> <sup>6</sup>	Australia and New Zealand	Frequency of use	Generic patient
1995	Mikuls and O'Dell <sup>5,b</sup>	USA	Initial prescriptions	Initial therapies; generic patient
1997	Mikuls and O'Dell <sup>5,b</sup>	USA	Initial prescriptions	Initial therapies; generic patient
1998	Maetzel <i>et al.</i> <sup>8</sup>	Canada and USA	Vignette/sequences sought after methotrexate failure	3 scenarios; increase in disease severity
1999	Mikuls and O'Dell <sup>5,b</sup>	USA	Initial prescriptions	Initial therapies; generic patient
2000	Erkan <i>et al.</i> <sup>10</sup>	USA	Vignette/initial prescriptions	6 scenarios; 3 disease states + 3 cost implications
2001	Pope <i>et al.</i> <sup>4a</sup>	Canada	Frequency of DMARD use	Looked at various patient characteristics, e.g. disease severity and age of patient
2002	Birmingham study	UK	DMARD sequence	Initial and ongoing therapy; generic patient

<sup>a</sup> Date of survey not given, approximated from submission date.  
<sup>b</sup> Same paper.

### Summary of papers

Survey papers are summarised in date order.

#### 1991

One paper from the UK: Kay and Pullar (1992)<sup>3</sup>

- Aim: to find out DMARD prescribing practice patterns in patients who had not previously received a DMARD.
- Methods: physician questionnaire, with sample drawn from UK consultant rheumatologists. Additional questions about drug monitoring practice.
- Quality: methods and sampling methodology were clearly described, except that the date of

the survey is not given. The response rate was 75%, but a small sample of 100. The preference estimate was based on the number of respondents choosing particular DMARDs.

- Results: physician preference: sulfasalazine was the overall drug of preference, with D-penicillamine, hydroxychloroquine, IM gold, methotrexate, oral gold and azathioprine cited as drugs that would be used as initial preference on occasion.
- Conclusion: out of seven DMARDs that are used as initial treatments, sulfasalazine was the overall drug of preference.

#### 1992

One paper from Canada: Collins and co-workers (1994)<sup>9</sup>

- Aim: to identify the initial choice of DMARD prescription among Canadian rheumatologists, given degrees of disease severity.
- Methods: five clinical scenarios representing progressively higher levels of severity were presented. Sample drawn from Canadian Rheumatism Association Directory. Additional questions asked about drug monitoring practice and dosing schedule.
- Quality: the methods and sampling methodology are clearly described. Response rate 79% (155/197). Preference estimate based on percentage of respondents choosing particular DMARDs.
- Results: physician preference (% of respondents choosing the given drug):
  - Scenario 1: IM gold (35.5%), antimalarial (28.4%), methotrexate (18.7%), sulfasalazine (9%), combination – antimalarial + methotrexate (3.2%), combination – antimalarial + IM gold (1.9%), auranofin (1.3%)
  - Scenario 2: antimalarial (51%), IM gold (16.1%), methotrexate (16.1%), sulfasalazine (13.5%), combination – antimalarial + methotrexate (1.9%), combination – antimalarial + IM gold (0.6%), combination – antimalarial + sulfasalazine (0.6%).
  - Scenario 3: IM gold (36.4%), methotrexate (35.1%), antimalarial (14.9%), sulfasalazine (5.8%), combination – antimalarial + IM gold (5.2%), D-penicillamine (0.6%), combination – IM gold + methotrexate (0.6%).
  - Scenario 4: methotrexate (34.9%), IM gold (34.2%), antimalarial (19.7%), sulfasalazine (5.3%), combination – antimalarial + IM gold (2%), auranofin (1.3%), D-penicillamine (1.3%), combination – antimalarial + methotrexate (1.3%).
  - Scenario 5: methotrexate (44.5%), IM gold (31.6%), combination – antimalarial + IM gold (5.2%), combination – IM gold + methotrexate (5.2%), combination – antimalarial + methotrexate (4.5%), sulfasalazine (2.65%), triple combination – antimalarial + methotrexate + IM gold (1.3%), antimalarial (1.3%), D-penicillamine (1.3%), combination – auranofin + methotrexate (0.6%), combination – azathioprine + methotrexate (0.6%), triple combination – antimalarial + methotrexate + sulfasalazine (0.6%).
- To summarise: five drugs were chosen, with IM gold, methotrexate and antimalarial therapy being the most preferred drugs. Their use as an initial therapy seems to depend on disease severity, with methotrexate being more commonly used as the severity of disease increases. These drugs were also

increasingly used in combination as the severity increased. Rheumatoid factor status, but not age, appeared to affect the prescribing pattern.

## 1994

Two surveys were undertaken in 1994: the first from France, and the second from Australia and New Zealand.

France: de Asit and co-workers (1996)<sup>7</sup>

- Aim: to identify how French office- and hospital-based rheumatologists treat early RA.
- Methods: three vignettes were used, corresponding to different degrees of severity. The physicians were asked about prescribing practice at presentation and at 1 year. All paper patients at presentation had a disease duration of 6 months, a definite RA diagnosis and no prior use of DMARDs.
  - Case 1 had multiple prognostic factors at presentation. At 1 year two outcomes were proposed: C1, a 50% deterioration; C2: a 50% improvement.
  - Case 2 presented with RA without poor prognostic factors but with a poor socio-economic situation. At year 1, she remained stable C1, or improved C2.
  - Case 3 was an 80-year-old male who at presentation had severe inflammation. At 1 year C1, he remained the same as at presentation or C2 improved.
- Quality: the methods are reasonably clear, but the sampling frame is unclear in that no details are given as to how or from where the sample was chosen. In addition, the response rate was just 58% (185/317).
- Results: physician preference
  - At presentation C0:
    - Case 1: 93% of respondents prescribed a DMARD [IM gold 55%, methotrexate 25%, tiopronin 9%, antimalarial (hydroxychloroquine) 7%, D-penicillamine 4%, sulfasalazine 2%].
    - Case 2: 86% of respondents prescribed a DMARD [IM gold 37%, antimalarial (hydroxychloroquine) 42%, tiopronin 7%, sulfasalazine 7%, methotrexate 6%].
    - Case 3: 40% of respondents prescribed a DMARD [IM gold 45%, antimalarial (hydroxychloroquine) 24%, sulfasalazine 12%, methotrexate 10%, tiopronin 5%, D-penicillamine 4%].
  - At 1 year C1:
    - Case 1: 50% deterioration; 99% of respondents prescribed a DMARD with 65% prescribing methotrexate. Just three respondents

prescribed combination therapy, with two of these using tiopronin/hydroxychloroquine and one using methotrexate/hydroxychloroquine.

- Case 2: stable; 97% of respondents prescribed DMARDs [IM gold 41%, methotrexate 18%, antimalarials (hydroxychloroquine) 4%].
- Case 3: stable: 67% of respondents prescribed a DMARD [IM gold 35%, methotrexate 24%, antimalarials (hydroxychloroquine) 13%, sulfasalazine 10%, D-penicillamine 6%].

At 1 year C2:

- Case 1: 50% improved; 87% of respondents continued with the same treatment as at C0, 7% discontinued the DMARD and 5% changed the DMARD.
- Case 2: improved; 96% of those who prescribed a DMARD therapy at C0 continued their initial prescription and none discontinued DMARD therapy.
- Case 3: improved, similar to presentation, 56% of respondents given a DMARD.
- In summary: in the case of deterioration the tendency was to switch from a less toxic to a more toxic drug (e.g. from hydroxychloroquine to gold and from gold to methotrexate). Where the outcome was favourable the tendency was towards a variation in practice, with, for example, 13% of respondents switching from an initially prescribed DMARD to another DMARD (5%) or discontinuing therapy. In case 3, DMARDs were started by 25% and stopped at C2 by 36%. Note: Where no DMARDs are given, the treatment was a mix of NSAID and steroid therapy.

Australia and New Zealand: Conaghan and co-workers (1997)<sup>6</sup>

- Aim: to assess self-reported prescribing habits of DMARDs and to determine by comparison with previous surveys whether changes in prescribing patterns had changed from the mid-1980s to the mid-1990s.
- Methods: postal questionnaire asking rheumatologists to name the most frequently used DMARDs in their practice that they viewed as their most effective in general, their most effective in treating aggressive disease and smouldering disease, and in young adults. As the 1989 and 1984 questionnaires were similar, results of all three surveys were compared. The samples were drawn from the directories of the Australian and New Zealand Rheumatology Association.
- Quality: the methods and sampling were clear; however, because the questionnaire had asked multiple questions some of the reporting of the results is difficult to interpret and few data are

given about the 1989 survey. The response rate in 1994 was 60% (171/284), compared with 51% in 1989 and 77% in 1984.

- Results: physician preference. The most popular drugs in 1994 were methotrexate (94% of respondents), sulfasalazine (91%) and antimalarials (60%). In 1984, gold (94%), D-penicillamine (89%) and antimalarials (54%) were the most popular choice of drugs. In addition, in 1994 methotrexate was named by the most respondents as their most effective drug (85%) and methotrexate was also the most popular drug for aggressive disease (80%). In 1994 sulfasalazine was the most popular drug of choice in young people (79%).
- Conclusion: a big change in prescribing practice occurred from 1984 to 1994, with methotrexate and sulfasalazine taking the place of gold and D-penicillamine. Antimalarials, however, remained over the 10 years a popular third choice of drug. In 1994, methotrexate appeared to be the drug of choice in aggressive disease, whereas in young people, practitioners prescribed sulfasalazine.

### 1995

Only one survey was undertaken in 1995, in the USA. The results are reported as part of a survey undertaken in 1999. Please see Mikuls and O'Dell,<sup>5</sup> below, for further details.

### 1996

One paper, by Maetzel and co-workers,<sup>8</sup> described a survey simultaneously undertaken in the USA and Canada.

- Aim: to determine which second line agents Canadian and US rheumatologists use to treat patients with active RA.
- Methods: three patient scenarios were given each of different disease severity, and physicians were asked to name their first and second choice DMARD.
  - Scenario 1: aggressive RA in a 38-year-old woman, DMARD naive, with 26 actively inflamed joints, six erosions, ESR and RF markedly elevated.
  - Scenario 2: moderate RA in a 32-year-old woman, DMARD naive, NSAIDs not helpful, six actively inflamed joints, no erosions, ESR and RF moderately elevated.
  - Scenario 3: aggressive RA failing methotrexate 25 mg = patient from scenario 1 failing treatment with methotrexate.

The survey also asked physicians about steroids, costs and, for the USA only, formulary restrictions.

The samples were drawn from the Canadian Rheumatology Association and the ACR.

- Quality: the methods and sampling frame are clear. A good response rate was achieved: Canada 87.8% (231/263) and USA 71.9% (230/320).
- Results:
  - Scenario 1 (Canada): methotrexate was drug of first choice (68.7% respondents), with 14.5% naming gold as first choice; 50% named gold as a second choice.
  - Scenario 1 (USA): methotrexate again was drug of first choice for the majority (78.5% of respondents). Second choice drugs were wide ranging (IM gold 24.8%, sulfasalazine 14%, azathioprine 12.6%, hydroxychloroquine 8.4%).
  - Scenario 2 (Canada): drug of first choice was wide ranging (hydroxychloroquine 47.2%, methotrexate 22%, gold 11.2%, sulfasalazine 7.9%), with drug of second choice being sulfasalazine (27.6%).
  - Scenario 2 (USA): two drugs of first choice given, hydroxychloroquine (39% of respondents) and methotrexate (38.8%): sulfasalazine remained the most popular drug of second choice (25.7%).
  - Scenario 3 (Canada): combination therapy, methotrexate and hydroxychloroquine was given by 41.1% of respondents as a drug of first choice, with 34.6% giving as first choice IM gold and 16.4% giving a combination of methotrexate and IM gold.
  - Scenario 3 (USA): no single agent emerged, with the largest number of respondents indicating they would use combination (38.3%) or triple therapy (23.8%) as a first choice. Most combinations use methotrexate plus either sulfasalazine (11.7%) or hydroxychloroquine (11.7%). The same agents also dominated triple therapy, with 21.5% of respondents nominating methotrexate plus hydroxychloroquine and sulfasalazine. Drugs of second choice were similar for both Canada and the USA. These were gold (21% Canada, 11.2% USA) and combination therapy MTX + HCQ (27.6% Canada, 28.5% USA). In addition, AZA was chosen by 13% of USA respondents.
- Conclusion: in aggressive disease in both the USA and Canada, methotrexate was the drug of first choice. In moderate RA in the USA the drugs of first choice were hydroxychloroquine and methotrexate, whereas in Canada a wide range of drugs was given (hydroxychloroquine, methotrexate, gold, sulfasalazine). Where

methotrexate failed, in the USA no single drug emerged, with just over one-third adding sulfasalazine and hydroxychloroquine to give combination therapy and one-fifth giving triple therapy, with the same agents being used (methotrexate, sulfasalazine, hydroxychloroquine). In Canada methotrexate and hydroxychloroquine was again the most popular choice, but one-third of respondents would stop methotrexate and give IM gold instead.

## 1999

One paper, by Mikules and O'Dell,<sup>5</sup> described a survey undertaken in 1999 and compared the results with similar surveys undertaken in 1997 and 1995.

- Aim: to determine which DMARD rheumatologists thought appropriate as initial therapy and to estimate which they would be likely to prescribe. In addition, information regarding prescribing practice of combination therapy was sought.
- Methods: physician questionnaire; 200 physicians chosen from a random sample of the ACR membership directory. The rheumatologists were asked which DMARDs were appropriate as initial therapies and which they were likely to prescribe as an initial monotherapy. Separately, they were asked whether they gave combination DMARDs as initial treatment and to estimate the number of patients currently treated with combination therapy. In addition they were asked to name the combinations that they used. The results from the three surveys were compared.
- Quality: methods and sampling methodology were clear, except that exclusions and identification non-responders were not stated. The response rate was 77% in 1995, 70% in 1997, and 57% in 1999.
- Results: the survey found that methotrexate was the most frequently prescribed monotherapy, with its popularity rising over time: 50% in 1995, 53% in 1997 and 64% in 1999. Hydroxychloroquine was the next most frequently prescribed DMARD, with 30% of respondents choosing it in 1999; however, no figures were given for 1997 and 1995. Sulfasalazine was reportedly prescribed by 5% of respondents, while IM gold and leflunomide accounted for less than 1% of positive answers. The paper deals with combination therapy in some detail and found that 47% of respondents in both 1999 and 1997 viewed combinations as an appropriate initial therapy (this question was

not asked in 1995). Ninety-seven per cent of respondents used combinations in practice in 1999, compared with 99% in 1997 and 90% in 1995. The most frequently prescribed combination was methotrexate + hydroxychloroquine, with methotrexate + sulfasalazine and sulfasalazine + hydroxychloroquine also being commonly prescribed.

- **Conclusions:** methotrexate appears to be the most popular single therapy prescribed as an initial therapy, but its use in combination appears to be popular. This paper demonstrates the importance of taking the phrase of the question into account when interpreting the results. For example, sulfasalazine was viewed by 89% of respondents as an appropriate initial therapy, but only prescribed by 5% of respondents when they were asked to estimate the amount of times they actually prescribed it.

## 2000

One paper from the USA, by Erkan and co-workers,<sup>10</sup> looked at prescribing practice in relation to disease severity and cost.

- **Aim:** to identify treatment preferences for first line therapy and determine whether severity of disease and pharmaco-economic variables modify physicians' choices.
- **Methods:** postal questionnaire to members of the ACR, identified from the 1999 directory and who were in adult practice. The questionnaire involved paper patients, all of whom were the same age and gender, 45-year-old women, who were initially presenting with mild, moderate and severe disease. Physicians were asked to identify their choices of first line therapy for each patient, (1) taking cost into consideration, (2) then not taking cost into consideration, (3) then identifying therapy that they would have chosen for themselves or a family member (to determine their optimal treatment). For analysis drugs were categorised into five groups: NSAIDs (including aspirin compounds), cyclooxygenase-2 inhibitors, corticosteroids – prednisolone, traditional DMARDs (HCQ, SSZ, AZA, CYC, AZA, D-Pen, gold and MTX) and new DMARDs (LEF and anti-TNF therapies, etanercept and infliximab). The chi-squared test was used to analyse the data. By comparing the number of individual medications and treatment regimens for each of the three questions, differences in prescribing patterns were identified.
- **Quality:** the methods and sampling frame are clear, but the response rate was low, at 37.7%

(375/994). In addition, there appears to be incomplete reporting of results.

- **Results:** hydroxychloroquine was the most commonly cited medication for mild disease activity at presentation. Methotrexate was the most commonly cited medication for moderate to severe disease activity. For severe disease activity when cost was not a consideration, 65% (217) of respondents included new DMARDs (LEF, etanercept and infliximab) in their choice of first line drugs; this number decreased to 14% (47) when cost was a consideration.
- **Conclusions:** in mild disease hydroxychloroquine is given, whereas methotrexate is given in severe disease; however, if cost is not a consideration anti-TNF is more likely to be given. There appears to be selective reporting in this paper and figures do not necessarily match up with the text conclusions. It is difficult for the reader to check the calculations; therefore, the conclusions and results are as stated in the paper.

## 2001

One paper, by Pope and co-workers,<sup>4</sup> reported on Canadian DMARD prescribing practice.

- **Aim:** to find the frequency of use of named DMARDs: antimalarials, methotrexate, sulfasalazine, gold, azathioprine, ciclosporin A and D-penicillamine.
- **Methods:** a postal questionnaire, sent to practising rheumatologists in adult care who were members of the Canadian Rheumatology Association. Physicians were asked to say which DMARDs they used and whether this use was 'frequently' or 'occasionally' or 'do not use'. The stage of the disease was not suggested.
- **Quality:** the methods of survey and sampling frame were clearly described, but the year of study had not been reported. Most of the results were reported in a histogram, except for methotrexate, hydroxychloroquine and sulfasalazine. It is unclear whether these three drugs were used 'frequently' or 'occasionally'. For the purposes of the following analysis, it is assumed that these drugs are being used 'frequently'. The response rate was 70% (195/279).
- **Results:** the study found that the most 'frequently' used DMARDs were methotrexate (100% of respondents), hydroxychloroquine (100%), sulfasalazine (98%), IM gold (40%), chloroquine (16%) azathioprine (9%), ciclosporin A (6%), D-penicillamine (2%) and oral gold (1%). Drugs used 'occasionally' were

azathioprine (74%), ciclosporin A (69%), IM gold (56%), D-penicillamine (45%) and oral gold (18%). Open questions were asked about other DMARDs in use. From these tetracycline or minocycline were named by 54% of respondents, with leflunomide named by 33% and anti-TNF by 13%. However, the leflunomide and anti-TNF figures should be regarded with caution, as they had not been released for use at the time of the first mailing of the survey. Combination therapy was stated to be 'frequently' used by 80% of respondents, with only 19% 'occasionally' using combination

therapy. The most popular combination was methotrexate + hydroxychloroquine, used by 61% of respondents, with methotrexate + hydroxychloroquine/sulfasalazine (15%) and methotrexate + sulfasalazine (8%) the next most popular combinations.

- Conclusions: three drugs were named as the most 'frequently' used drugs by nearly all of respondents: methotrexate, hydroxychloroquine and sulfasalazine. In addition, 80% of respondents would 'frequently' use combination therapy, with the most popular combinations using the above three drugs.

## Appendix 3

### Current treatment practice using DMARDs

This questionnaire is designed to provide a snapshot of current practice in adult rheumatology. Please fill it in to reflect your practice within current constraints, rather than what you would consider ideal treatment. This should take about 3 minutes.

All responses will be treated in strictest confidence. This research will inform a review currently commissioned by NHS R&D.

1. In patients with newly diagnosed RA.

**Which DMARDs are you most likely to give as first-line therapy?**

*(Please rank in order of preference with 1 being your first choice)*

Drug	Rank
Anti-TNF	
Azathioprine	
Chloroquine	
Cyclosporin	
D-Penicillamine	
Gold IM	
Gold Oral	
Hydroxychloroquine	
IL-1ra (Anakinra)	
Leflunomide	
Methotrexate Oral	
Methotrexate Parenteral	
Sulphasalazine	
Other <i>(please specify which drugs)</i> ..... .....	
Combination <i>(please specify which drugs)</i> ..... .....	

Can you estimate approximately for what percentage of newly diagnosed patients you would choose the therapy you ranked as 1?

	Please tick one
<b>Less than 25%</b>	
<b>26 to 50%</b>	
<b>51 to 75%</b>	
<b>Over 75%</b>	

2. Failed response

Patients often fail several DMARDs, please can you tell us a typical DMARD sequence you might use

**First line drug/s** .....

**Second line drug/s** .....

**Third line drug/s** .....

**Fourth line drug/s** .....

**Fifth line drug/s** .....

**Sixth line drug/s** .....

3. Influences on Treatment Patterns

Many things influence treatment patterns.

*(Please circle your level of agreement with the following statement for each of the factors listed)*

“THE FOLLOWING FACTOR MAY INFLUENCE MY CHOICE OF DMARD”	<b>LEVEL OF AGREEMENT</b>				
<b>Rheumatoid factor status</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice	..... .....				
<b>Erosions at diagnosis</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice	..... .....				
<b>Number of joints involved</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice	..... .....				
<b>Episodic versus persistent symptoms</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice	..... .....				
<b>Need for rapid symptom control (e.g. patient distress, job context, social role)</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice	..... .....				



“THE FOLLOWING FACTOR MAY INFLUENCE MY CHOICE OF DMARD”	LEVEL OF AGREEMENT				
<b>Manual versus sedentary occupation</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice					
.....					
.....					
<b>Drug cost</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice					
.....					
.....					
<b>A high acute phase reaction</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice					
.....					
.....					
<b>Side effect profile of drug</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice					
.....					
.....					
<b>Age of patient</b>	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If you agree please specify in what way this might affect your choice					
.....					
.....					
What other important factors might influence your choice?					
.....					
.....					
.....					
.....					
Finally – could you give the year that you graduated from med school .....					

*Thank you for your time and help.*



## Appendix 4

# The Delphi version of the BRAM

### User's guide to the BRAM

The BRAM uses a random number generator described by Knuth.<sup>61</sup> This model was built to be used by its author. It has not been possible to make it fully user friendly. The model runs under suitably recent versions of Windows as a stand-alone executable file. To run the model, it is essential that the data files listed below are in the same directory as the executable file itself.

The data files are all in comma-separated value (CSV) format. They can be modified in either a spreadsheet or a text editor. It is, however, essential that they are saved in CSV format and that the number of rows and columns is not changed. If any file is missing, or too short, the program will not run, while if the structure is changed in any other way, the program may produce meaningless results.

The data files required are as shown in *Table 29*.

### Details of the data files

#### Age2Prob

This file contains general population survival curves. The ones supplied are recent UK life tables from the Office of National Statistics. They may be readily changed to fit other countries' data sets. The first column should not be altered. The second and third columns represent the proportion of live births surviving to a given exact age in years. Survival has been truncated to the age of 101. It is essential that each column contains a decreasing sequence of numbers. The program will probably run correctly if survival is truncated to a slightly earlier age, but not below 85.

#### RAOnsAge

The second column should be left unchanged. The first column contains cumulative proportions, which should run from 0 to 1. Suppose the

**TABLE 29** Data files needed for the BRAM

Filename	Rows	Columns	Contents
Age2Prob	102	3	General population survival curves
DMARDsa	12	2	Parameters for Weibull distributions of time on DMARDs
DMARDsb	12	2	
RACStart	13	2	Start-up costs associated with treatment
RACUse	13	2	Steady-state annual costs associated with treatment
RADivDMA	16	2	DMARD number of divergence
RAHAQ2MR	25	2	Effect of HAQ on mortality
RAHAQch	13	2	Average time to HAQ change on treatment
RAHAQcst	25	2	Offset costs according to HAQ
RAHAQimp	13	2	HAQ improvement on starting treatment
RAHAQini	24	2	Distribution of initial HAQ states
RAHAQJR	25	2	Effect of joint replacement on HAQ
RAJrb	25	3	<i>b</i> parameter for Weibull distribution of time to joint replacement according to HAQ
RAOnsAge	15	2	Initial distribution of age and gender
RAStrLen	16	2	Number of DMARDs in each strategy
RAStrLst	12	17	List of strategies
RAToxic	13	4	Parameters for toxicity calculations
RAToxMat	13	2	0–1 variable for whether toxicity of a particular DMARD matters
RAVars	12	2	Other system variables

**TABLE 30** Initial distribution of age and gender

Age	15–25	25–35	35–45	45–55	55–65	65–75	75–85
Male	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>
Female	<i>h</i>	<i>k</i>	<i>m</i>	<i>n</i>	<i>p</i>	<i>q</i>	<i>r</i>

distribution among the population is as shown in *Table 30*.

Then the value of  $a$  should appear opposite the number 25,  $a + b$  opposite 35, and so on. The value of  $a + b + c + d + e + f + g + h$  appears opposite the number 95, etc.

### RAHAQcst

This file contains the offset costs associated with HAQ scores. The first column should be unchanged, and gives all possible values of HAQ score. The second column gives the offset cost for each HAQ score. The supplied values were calculated as  $860HAQ$ . Note that these can be included or excluded from the calculations using a check-box on the screen.

### RAHAQini

This file contains the distribution of initial HAQ scores. The first column should be unchanged, and gives all possible values of HAQ score. The second column gives the proportion starting with each HAQ score. These numbers must add to 1.

### RAHAQ2MR

This table converts HAQ score to mortality ratio. The first column should be unchanged, and gives all possible values of HAQ score. The second column gives the corresponding mortality ratio for each HAQ score. The supplied values are calculated as  $1.33^{HAQ}$ .

### Files relating to particular treatments

The model is designed to allow for 11 different DMARDs and one form of combination therapy. Patients who have no DMARDs remaining are given palliative therapy. The treatments in the model are numbered as shown in *Table 31*.

**TABLE 31** Treatments available in the BRAM

Number	Treatment
0	Palliation (Pall)
1	Anakinra (Aka)
2	Azathioprine (AZA)
3	Ciclosporin (CyA)
4	Etanercept (Etan)
5	Gold (GST)
6	Hydroxychloroquine (HCQ)
7	Infliximab (Infl)
8	Leflunomide (LEF)
9	Methotrexate (MTX)
10	Penicillamine (DPen)
11	Sulfasalazine (SSZ)
12	Combination (CyA + MTX)

Although the model allows for variation in strategy, the present version assumed that only the above DMARDs are used. (It would, of course, be possible to substitute the values for a new DMARD in place of any of those used.)

### RACStart, RACUse

These two files relate to the costing associated with the use of DMARDs. It is assumed that early extra costs can be regarded as a one-off cost applied at the time of starting a treatment. In each file, the first column gives the treatment numbers from 0 to 12 and should not be changed, while the second file gives the relevant costs. As an example, the cost for azathioprine was calculated as £2017.24 for the first year (including all pretreatment tests) and £1332.52 for each subsequent year. The steady-state annual costs are thus £1332.52, while the start-up costs are calculated as  $£2017.24 - £1332.52 = £684.72$ .

### DMARDsa, DMARDsb

These files relate to the time spent on each DMARD and are unlikely to need changing.

### RAHAQch

This file gives the average time to a minimum measurable deterioration (0.125 increase) in HAQ, varied by treatment.

### RAHAQimp

This file gives the improvement (decrease) in HAQ on starting a DMARD.

### RAHAQJR, RAJRb

These two files relate to joint replacement. At present, it is recommended that these files should be left unaltered.

### RAToxic, RAToxMat

These files relate to the procedures necessary to ensure that combination therapy is not offered if either CyA or MTX was quit on grounds of toxicity and should not be altered.

### RAVars

This file contains other system variables. The first column contains the values of these variables, while the second column contains a description. The second column should not be altered, and it is important to keep the rows in the right order. Most of the values relate to joint replacement, and can be ignored (but not omitted from the file). Variables that can be changed are as follows.

- *Discount rates:* the default values relate to standard UK practice of discounting costs at 6%

and benefits at 1.5%. These are given as discount factors of 1.06 and 1.015, respectively. Similarly, a discount rate of 3% would be represented by a discount factor of 1.03, etc. A positive discount rate must be used. The program will fail if a discount factor of 1 is entered.

- *Conversion from HAQ to quality of life score:* the data set is based on the equation  $QoL = 0.862 - 0.327HAQ$ . The model assumes a linear relation, but the coefficients may be changed as required. Note that the negative sign on the 'slope' of the equation is included.
- *Start and end effects:* the model works on the basis that HAQ will improve gradually when a new treatment is started, and decline gradually until it is stopped. This is accounted for by a one-off deduction from the total QALYs applied on starting and ending each treatment. By default, the deduction is equal to 0.2 years' worth of the quality of life change on starting or finishing treatment. The figure 0.2 may be changed as required.

### RADivDMA, RAStrLen, RAStrLst

These files are the method of entering the different strategies into the model. When comparing two strategies, the decision point is the point of divergence between the strategies. Only patients reaching the point of divergence are counted, and, for such patients, costs and QALYs are accumulated from, and discounted to, the point of divergence. Thus, from the modelling point of view, a strategy consists of a sequence of DMARDs, one of which is identified as the 'divergence DMARD'. In the current version of the model, it is not possible for combination therapy to be the divergence DMARD: it is intended to remove this limitation in future versions of the model.

The model allows for a total of 16 strategies, numbered from 1 to 16. To use the model to compare two or more strategies, the strategies must be assigned consecutive numbers. Appropriate entries must be made in the three data files: no consistency checks are made in running the model. (This cumbersome procedure was caused by the desire to maintain compatibility with the DATA version of the model and it is intended to remove it at some point in the future.)

### Example of how to fill in the data files for strategies

Suppose it is desired to compare the three strategies shown in *Table 32*.

Strategy A diverges from the other two at the third line, but strategies B and C only diverge at the fourth line. It is thus necessary to run each of strategies B and C twice, allowing for the different divergence points. In allocating strategy numbers, it is generally expected that the more expensive and more effective strategy will be put first. Let us assume that strategy numbers are allocated as follows:

- 1 – Strategy A (divergence at third line)
- 2 – Strategy B (divergence at third line)
- 3 – Strategy C (divergence at third line)
- 4 – Strategy B (divergence at fourth line)
- 5 – Strategy C (divergence at fourth line).

Then the various files can be filled as follows.

### RADivDMA

This file has two columns. The first gives the strategy numbers and should be left unchanged. The second shows the divergence DMARDs. In this case, the first five rows should read as shown in *Table 33*.

The remainder of the file can be left unchanged, but must not be deleted.

### RAStrLen

Again, this file has two columns. The first gives the strategy numbers and should be left unchanged. The second shows the number of DMARDs in each strategy. In this case, the first five rows should read as shown in *Table 34*.

**TABLE 32** Example of strategies to be compared

Strategy A	Strategy B	Strategy C
SSZ	SSZ	SSZ
MTX	MTX	MTX
Etan	LEF	LEF
LEF	Etan	GST
GST	GST	AZA
AZA	AZA	CyA
CyA	CyA	Comb
Comb	Comb	

**TABLE 33** Example of list of divergence DMARDs

1	4
2	8
3	8
4	4
5	5
4, Etan; 5, GST; 8, LEF	

**TABLE 34** Example of list of strategy lengths

1	8
2	8
3	7
4	8
5	7

**TABLE 35** Example of list of strategies

1	12	12	12	12	12
2	3	3	3	3	3
3	2	2	2	2	2
4	5	5	5	5	5
5	8	4	8	4	8
6	4	8	9	8	9
7	9	9	11	9	11
8	11	11	0	11	0
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0

Again, the remainder of the file can be left unchanged, but must not be deleted.

### RAStrLst

This file has 12 rows and 17 columns. The first column contains the numbers from 1 to 12, and represents the number of DMARDs left. Each other column represents a single strategy, column B for strategy 1, column C for strategy 2, etc. Note that the strategy numbers do not appear in this file. In each column, the DMARDs in a strategy appear in reverse order, with the last DMARD in row 1, etc. Thus, in our case, the first six columns of the table should look like *Table 35*.

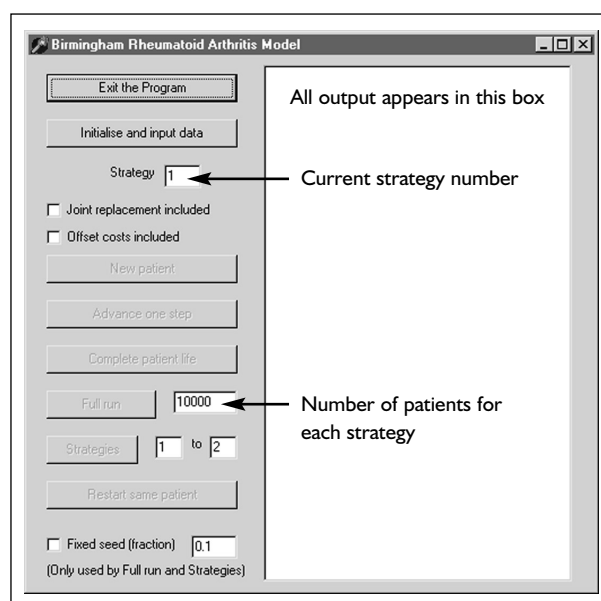
Yet again, the remainder of the file can be left unchanged, but must not be deleted.

### Important note

If you have amended any of the data files using a package such as Excel, the files must be saved in CSV format, and must be closed before the program is run.

### How to run the model

When the program is run, the screen depicted in *Figure 6* appears, with most of the command buttons disabled. The button 'Initialise and input data' must be pressed to enable other commands. The detailed running of the program may then be seen by using the buttons 'New patient', 'Advance one step', 'Complete patient life' and 'Restart same patient'.

**FIGURE 6** The BRAM user interface

The model can be run with or without joint replacements, and with or without offset costs. Data on the effect of joint replacement on HAQ is of poor quality, and it is recommended that 'Joint replacement included' should be left unchecked.

To obtain usable results, the 'Full run' and 'Strategies' buttons must be used. The 'Full run' button runs a single strategy, while the 'Strategies' button runs any set of consecutively numbered strategies. The input box to the right of the 'Full run' button contains the number of patients to be run for each strategy.

While the program is running, totals are printed in the output box every 1000 patients. At the end of a run of consecutive strategies, differences in costs and QALYs and ICERs are printed for each pair of strategies, together with quasi-confidence intervals.

Following the example above, the program can be run from strategies 1 to 5. The meaningful comparisons will be 1–2 (A–B), 1–3 (A–C), and 4–5 (B–C): the other output comparisons are meaningless and should be ignored.

To obtain repeatable output, the 'Fixed seed' check-box must be checked. The default seed value 0.1 may be replaced (but will then give a different set of output). Permitted values for the seed are fractions between 0 and 1 (exclusive): other values will be ignored as if the box were not checked.

In the interests of transparency of modelling, the source code is listed below.

```

unit Fram1;
{this code has been written assuming input in the correct format}
{no checks are made for incorrectly formatted files}
{code has been developed gradually and is not guaranteed optimal}
{procedures are initiated by clicking on buttons only}

interface

uses
  Windows, Messages, SysUtils, Classes, Graphics, Controls, Forms, Dialogs, StdCtrls;

type
  TForm1 = class(TForm)
    Button1: TButton;
    Button2: TButton;
    Edit1: TEdit;
    ListBox1: TListBox;
    Button3: TButton;
    Label1: TLabel;
    Button4: TButton;
    Button5: TButton;
    Button6: TButton;
    Edit2: TEdit;
    CheckBox1: TCheckBox;
    Button7: TButton;
    Button8: TButton;
    Edit3: TEdit;
    Label2: TLabel;
    Edit4: TEdit;
    CheckBox2: TCheckBox;
    Edit5: TEdit;
    Label3: TLabel;
    CheckBox3: TCheckBox;
    procedure Button1Click(Sender: TObject);
    procedure Button2Click(Sender: TObject);
    procedure Button3Click(Sender: TObject);
    procedure Button4Click(Sender: TObject);
    procedure Button5Click(Sender: TObject);
    procedure Button6Click(Sender: TObject);
    procedure Button7Click(Sender: TObject);
    procedure Button8Click(Sender: TObject);
  private
    { Private declarations }
  public
    { Public declarations }
  end;

const ranA = 62089911;
      ranM = 2147483647;
      snstart = 1;
      snStartNewTreatment = 2;
      snOnTreatment = 3;
      snQuitDMARD = 4;
      snSelectNextTreatment = 5;
      snJointReplacement = 6;
      snDeath = 7;
      snInclude = 8;

var
  CStart:array[0..25] of real;
  CUse:array[0..25] of real;
  DMARDsa:array[0..23] of real;

```

```

DMARDsb:array[0..23] of real;
RAAge2Prob:array[0..305] of real;
RADivDMARD:array[0..31] of real;
RAHAQ2MR:array[0..49] of real;
RAHAQch:array[0..25] of real;
RAHAQcst:array[0..49] of real;
RAHAQimp:array[0..25] of real;
RAHAQini:array[0..47] of real;
RAHAQJR:array[0..49] of real;
RAJrb:array[0..74] of real;
RAOnsetAge:array[0..29] of real;
RAStratLength:array[0..31] of real;
RAStratList:array[0..203] of real;
RAToxicity:array[0..51] of real;
RAToxMat:array[0..25] of real;
RAVars:array[0..23] of real;
nextstatelist:array[1..15] of string;
DMARDnames:array[0..12] of string;
allcmean,allcse,allumean,alluse:
  array[1..50] of real;
lasttreatment:array[1..50,0..12] of integer;
cJR,
cTotAbsolute,cTotDiscount,
DiscRateCosts,DiscRateUtils,
HAQ2QoLa,HAQ2QoLb,HAQcurrent,
HAQshift,
JRRiska,JRRiskb,JRRiskt0,
JRRiska1,JRRiska2,
pDeathJR,pFailJR,pRepeatJR,
SMR,
thiscmean,thiscse,thisumean,thisuse,
tAge,tAgeNextDMARD,tAtRiskJR,
tEndLoss,tStartLoss,tDeath,tHospital,tHospitalEnd,
tJR,tChange,tHAQchange,
tTotal,tThisDMARD,tNextDMARD,
uQoLCurrent,uTotAbsolute,uTotDiscount,
zzDebug1,zzDebug2
  :real;
ranseeds,aaStrategy,JRcount,JRcol,abJRon,
storedseed,
nDMARDsLeft,nThisDMARD,
zDivReached,zLocation,zSex,zToxicity,zDead,
nextstate,callstoRNG,negchange,rejects
  :integer;
{zSex = 1 for male, 2 for female}
Form1: TForm1;

```

implementation

```

{$R *.DFM}
function standarduniform: real;
{generates sample from standard uniform distribution using}
{a linear congruential generator}
{the value of ranM is large enough for reasonable samples}
{the value of ranA is optimal for this ranM in a sense}
{described in Knuth DE, The Art of Computer Programming}
{3rd edition, Volume 2, Seminumerical Algorithms, p. 108}
{total number of calls to this function maintained for}
{checking that repeats have not occurred}
var i:int64;
begin
  callstoRNG:=callstoRNG+1;

```



```

i:=ranseeds;
i:=i*ranA;
i:=i mod ranM;
ranseeds:=i;
result:=i/ranM
end;

function power(x,y:real):real;
{this function calculates x to power y}
begin
  if x>0 then
    result:=exp(y*ln(x))
  else
    result:=0;
end;

procedure file2table(n:string; var a:array of real; j1,j2:integer);
{one-dimensional arrays used for ease of passing arrays as arguments}
{to procedures: rows 0 to j1, columns 0 to j2}
{co-ordinates converted throughout}
{this procedure reads in a CSV file to the given array}
var f:file of char;
    c:char;
    s:string;
    k,k2,k3:integer;
    x:real;
begin
  AssignFile(f,n);
  reset(f);
  for k:=0 to j1 do
  begin
    for k2:=0 to j2 do
    begin
      Read(f,c);
      s:='';
      repeat
        if ord(c)>32 then s:=s+c;
        Read(f,c);
      until ((c=chr(13)) or (c=','));
      val(s,x,k3);
      a[k+k2*(1+j1)]:=x;
    end;
  end;
  close(f);
end;

function distsamp(a:array of real; i:integer):real;
{this function samples from a distribution stored in an array}
{with rows numbered from 0 to i}
{values in first column, probabilities in second}

var j:integer;
    x,y,p:real;
begin
  p:=standarduniform;
  x:=0;
  for j:=0 to i do
  begin
    if x<p then y:=a[j];
    x:=x+a[i+1+j];
  end;
  result:=y;
end;

```

```

function linint(x:real; a:array of real; i,j1,j2:integer):real;
{this function is used for lookup in a table with rows numbered from}
{0 to i, value x to be found in column j1 and answer in column j2}
{linear interpolation is used if x is between values}
{each column may be either increasing or decreasing but must be}
{one or the other}
{if x is off the range of values in column j1, then the nearest}
{extreme is used}
var k:integer;
    sg,w,y,z:real;
begin
  y:=a[0+j1*(1+i)];
  z:=a[i+j1*(1+i)];
  if z>y then sg:=1 else sg:=-1;
  if sg*x<=sg*y then
  begin
    result:=a[0+j2*(1+i)];
  end
  else
  begin
    if sg*x>=sg*z then
    begin
      result:=a[i+j2*(1+i)];
    end
    else
    begin
      k:=0;
      repeat
        k:=k+1;
        w:=a[k+j1*(1+i)]
      until (sg*x<sg*w);
      y:=a[k-1+j1*(1+i)];
      result:=a[k-1+j2*(1+i)]+(x-y)*(a[k+j2*(1+i)]-a[k-1+j2*(1+i)])/(w-y);
    end
  end;
end;

procedure readandinit;
{this procedure reads all the data from the appropriate files into the}
{relevant arrays}
{it also initialises the event names and single variable parameters}
{and enables the buttons which run the model}
{all data should be contained in the relevant CSV files}
{except for current strategy and joint replacement switch}
var x:real;
begin
  Form1.ListBox1.Clear;
  x:=time;
  ranseeds:=trunc(x*ranM);
  file2table('RACStart.csv',CStart,12,1);
  file2table('RACUse.csv',CUse,12,1);
  file2table('DMARDSa.csv',DMARDSa,11,1);
  file2table('DMARDSb.csv',DMARDSb,11,1);
  file2table('Age2Prob.csv',RAAge2Prob,101,2);
  file2table('RADivDMA.csv',RADivDMARD,15,1);
  file2table('RAHAQ2MR.csv',RAHAQ2MR,24,1);
  file2table('RAHAQch.csv',RAHAQch,12,1);
  file2table('RAHAQcst.csv',RAHAQcst,24,1);
  file2table('RAHAQimp.csv',RAHAQimp,12,1);
  file2table('RAHAQIni.csv',RAHAQini,23,1);
  file2table('RAHAQJR.csv',RAHAQJR,24,1);
  file2table('RAJRb.csv',RAJRb,24,2);

```

```

file2table('RAOnsAge.csv',RAOnsetAge,14,1);
file2table('RAStrLen.csv',RAStratLength,15,1);
file2table('RAStrLst.csv',RAStratList,11,16);
file2table('RAToxic.csv',RAToxicity,12,3);
file2table('RAToxmat.csv',RAToxmat,12,1);
file2table('RAVars.csv',RAVars,11,1);
nextstatalist[snstart]:='Start';
nextstatalist[snStartnewTreatment]:='Start New Treatment';
nextstatalist[snOnTreatment]:='On Treatment';
nextstatalist[snQuitDMARD]:='Quit DMARD';
nextstatalist[snSelectNextTreatment]:='Select Next Treatment';
nextstatalist[snJointReplacement]:='Joint Replacement';
nextstatalist[snDeath]:='Death';
nextstatalist[snInclude]:='Include';
DMARDnames[0]:='Pall';
DMARDnames[1]:=' Ana';
DMARDnames[2]:=' AZA';
DMARDnames[3]:=' CyA';
DMARDnames[4]:=' Etan';
DMARDnames[5]:=' GST';
DMARDnames[6]:=' HCQ';
DMARDnames[7]:=' Infl';
DMARDnames[8]:=' LEF';
DMARDnames[9]:=' MTX';
DMARDnames[10]:='DPen';
DMARDnames[11]:=' SSZ';
DMARDnames[12]:='Comb';
cJR:=RAVars[0];
DiscRateCosts:=ln(RAVars[1]);
DiscRateUtils:=ln(RAVars[2]);
HAQ2QoLa:=RAVars[3];
HAQ2QoLb:=RAVars[4];
JRRiska1:=RAVars[5];
JRRiska2:=RAVars[6];
pDeathJR:=RAVars[7];
pFailJR:=RAVars[8];
pRepeatJR:=RAVars[9];
tEndLoss:=RAVars[10];
tStartLoss:=RAVars[11];
Form1.Button3.Enabled:=true;
Form1.Button5.Enabled:=true;
Form1.Button6.Enabled:=true;
Form1.Button8.Enabled:=true;
callstoRNG:=0;
negchange:=0;
rejects:=0;
end;

procedure showtrackers;
{this procedure displays the current values of all tracker variables}
{in the list box on the screen}
{it is used for verification of the model in one-step running mode}
{but is not called when a full sample is run}
var s:string;
begin
  Form1.ListBox1.Clear;
  s:=Format('aaStrategy %8d',[aaStrategy]);
  Form1.ListBox1.Items.Add(s);
  s:=Format('cTotAbsolute %10.2f',[cTotAbsolute]);
  Form1.ListBox1.Items.Add(s);
  s:=Format('cTotDiscount %10.2f',[cTotDiscount]);
  Form1.ListBox1.Items.Add(s);

```

```

s:=Format('HAQcurrent %10.4f',[HAQcurrent]);
Form1.ListBox1.Items.Add(s);
s:=Format('HAQshift %10.4f',[HAQshift]);
Form1.ListBox1.Items.Add(s);
s:=Format('JRRiska %10.4f',[JRRiska]);
Form1.ListBox1.Items.Add(s);
s:=Format('JRRiskb %10.4f',[JRRiskb]);
Form1.ListBox1.Items.Add(s);
s:=Format('nDMARDsLeft %8d',[nDMARDsLeft]);
Form1.ListBox1.Items.Add(s);
s:='ThisDMARD '+DMARDnames[nThisDMARD];
Form1.ListBox1.Items.Add(s);
s:=Format('SMR %10.4f',[SMR]);
Form1.ListBox1.Items.Add(s);
s:=Format('tAge %10.4f',[tAge]);
Form1.ListBox1.Items.Add(s);
s:=Format('tAgeNextDMARD%10.4f',[tAgeNextDMARD]);
Form1.ListBox1.Items.Add(s);
s:=Format('tAtRiskJR %10.4f',[tAtRiskJR]);
Form1.ListBox1.Items.Add(s);
s:=Format('tChange %10.4f',[tChange]);
Form1.ListBox1.Items.Add(s);
s:=Format('tDeath %10.4f',[tDeath]);
Form1.ListBox1.Items.Add(s);
s:=Format('tHAQchange %10.4f',[tHAQchange]);
Form1.ListBox1.Items.Add(s);
s:=Format('tJR %10.4f',[tJR]);
Form1.ListBox1.Items.Add(s);
s:=Format('tNextDMARD %10.4f',[tNextDMARD]);
Form1.ListBox1.Items.Add(s);
s:=Format('tThisDMARD %10.4f',[tThisDMARD]);
Form1.ListBox1.Items.Add(s);
s:=Format('tTotal %10.4f',[tTotal]);
Form1.ListBox1.Items.Add(s);
s:=Format('uQoLCurrent %10.4f',[uQoLCurrent]);
Form1.ListBox1.Items.Add(s);
s:=Format('uTotAbsolute %10.4f',[uTotAbsolute]);
Form1.ListBox1.Items.Add(s);
s:=Format('uTotDiscount %10.4f',[uTotDiscount]);
Form1.ListBox1.Items.Add(s);
s:=Format('zDead %8d',[zDead]);
Form1.ListBox1.Items.Add(s);
s:=Format('zDivReached %8d',[zDivReached]);
Form1.ListBox1.Items.Add(s);
s:=Format('zSex %8d',[zSex]);
Form1.ListBox1.Items.Add(s);
s:=Format('zToxicity %8d',[zToxicity]);
Form1.ListBox1.Items.Add(s);
{Keep on standby for future debugging
s:=Format('zzDebug1 %10.4f',[zzDebug1]);
Form1.ListBox1.Items.Add(s);
s:=Format('zzDebug2 %10.4f',[zzDebug2]);
Form1.ListBox1.Items.Add(s);
}
s:='Next Event '+nextstatelist[nextstate];
Form1.ListBox1.Items.Add(s);
end;

procedure newpatient;
{this procedure corresponds to the node start}
var i:integer;
    x:real;
    s:string;

```

```

begin
{the current value of ranseeds is stored to allow the patient}
{to be re-run for checking purposes}
  storedseed:=ranseeds;
  s:=Form1.Edit1.Text;
  val(s,aaStrategy,i);
  if Form1.CheckBox1.Checked then
    abJRon:=1
  else
    abJRon:=0;
  x:=standarduniform;
  x:=linint(x,RAOnsetAge,14,0,1);
  if x<85 then tAge:=x else tAge:=x-70;
  zDead:=0;
  zDivReached:=0;
  if x<85 then zSex:=1 else zSex:=2;
  zToxicity:=0;
  cTotAbsolute:=0;
  cTotDiscount:=0;
  HAQcurrent:=distsamp(RAHAQini,23);
  nDMARDSLeft:=round(linint(aaStrategy,RAStratLength,15,0,1));
  tTotal:=0;
  uTotAbsolute:=0;
  uTotDiscount:=0;
  JRcol:=1;
  JRRiska:=JRRiska1;
  nThisDMARD:=round(linint(nDMARDSleft,RAStratList,11,0,aaStrategy));
  tAtRiskJR:=0;
  JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
  nextstate:=snStartnewTreatment;
end;

procedure startnewtreatment;
var x,a,b:real;
begin
  {the following two lines give a standard exponential distribution}
  x:=standarduniform;
  x:=-ln(1-x);
  tThisDMARD:=0;
  if nThisDMARD=round(linint(aaStrategy,RADivDMARD,15,0,1)) then
  begin
    tTotal:=0;
    zDivReached:=1;
    cTotAbsolute:=linint(nThisDMARD,CStart,12,0,1);
    cTotDiscount:=linint(nThisDMARD,CStart,12,0,1);
    HAQshift:=linint(nThisDMARD,RAHAQimp,12,0,1);
    if HAQshift>HAQcurrent then HAQshift:=HAQcurrent;
    if nThisDMARD=0 then
      tAgeNextDMARD:=200
    else
      begin
        a:=linint(nThisDMARD,DMARDSa,11,0,1);
        b:=linint(nThisDMARD,DMARDSb,11,0,1);
        tAgeNextDMARD:=tAge+b*power(x,(1/a));
      end;
    HAQcurrent:=HAQcurrent-HAQshift;
    x:=HAQshift*HAQ2QoLb;
    uTotAbsolute:=tStartLoss*x;
    uTotDiscount:=tStartLoss*x;
    JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
    nextstate:=snOnTreatment
  end
end

```

```

else
begin
  cTotAbsolute:=cTotAbsolute+linint (nThisDMARD,CStart,12,0,1);
  cTotDiscount:=cTotDiscount
    +linint (nThisDMARD,CStart,12,0,1)*exp(-DiscRateCosts*tTotal);
  HAQshift:=linint (nThisDMARD,RAHAQimp,12,0,1);
  if HAQshift>HAQcurrent then HAQshift:=HAQcurrent;
  if nThisDMARD=0 then
    tAgeNextDMARD:=200
  else
  begin
    a:=linint (nThisDMARD,DMARDsa,11,0,1);
    b:=linint (nThisDMARD,DMARDsb,11,0,1);
    tAgeNextDMARD:=tAge+b*power(x,(1/a));
  end;
  HAQcurrent:=HAQcurrent-HAQshift;
  x:=HAQshift*HAQ2QoLb;
  uTotAbsolute:=uTotAbsolute+tStartLoss*x;
  uTotDiscount:=uTotDiscount+tStartLoss*x*exp(-DiscRateUtils*tTotal);
  JRRiskb:=linint (HAQcurrent,RAJRb,24,0,JRcol);
  nextstate:=snOnTreatment
end
end;

procedure ontreatment;
var x1,x2,x3,x4,x5,xcost:real;
begin
  x1:=standarduniform;
  x2:=linint (tAge,RAAge2Prob,101,0,zSex);
  x3:=standarduniform;
  x3:=-ln(1-x3);
  x4:=power((tatRiskJR/JRRiskb),JRRiska);
  SMR:=linint (HAQcurrent,RAHAQ2MR,24,0,1);
  tNextDMARD:=tAgeNextDMARD-tAge;
  tDeath:=linint (power(x1,1/SMR)*x2,RAAge2Prob,101,zSex,0)-tAge;
  if HAQcurrent=3 then
    tHAQchange:=200
  else
  begin
    x5:=standarduniform;
    x5:=-ln(1-x5);
    tHAQchange:=linint (nThisDMARD,RAHAQch,12,0,1)*x5;
  end;
  if abJRon=0 then
    tJR:=200
  else
    tJR:=power((x3+x4),(1/JRRiska))*JRRiskb-tAtRiskJR;
  uQoLcurrent:=HAQ2QoLa+HAQ2QoLb*HAQcurrent;
  if tDeath<tNextDMARD then tChange:=tDeath else tChange:=tNextDMARD;
  if tHAQchange<tChange then tChange:=tHAQchange;
  if tJR<tChange then tChange:=tJR;
  {check that time is going forwards}
  if tChange<0 then negchange:=negchange+1;
  xcost:=linint (nThisDMARD,CUse,12,0,1);
  {include offset costs if required}
  if Form1.CheckBox3.Checked then
    xcost:=xcost+linint (HAQcurrent,RAHAQcst,24,0,1);
  cTotAbsolute:=cTotAbsolute+tChange*xcost;
  cTotDiscount:=cTotDiscount
    +xcost*(exp(-DiscRateCosts*tTotal)/DiscRateCosts)
    *(1-exp(-DiscRateCosts*tChange));
  uTotAbsolute:=uTotAbsolute+tChange*uQoLcurrent;

```

```

uTotDiscount:=uTotDiscount
+uQoLcurrent
*(exp(-DiscRateUtils*tTotal)/DiscRateUtils)
*(1-exp(-DiscRateUtils*tChange));
tAge:=tAge+tChange;
tAtRiskJR:=tAtRiskJR+tChange;
tThisDMARD:=tThisDMARD+tChange;
tTotal:=tTotal+tChange;
if tDeath=tChange then
  nextstate:=snDeath
else if tHAQchange=tChange then
begin
  HAQcurrent:=HAQcurrent+0.125;
  JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
  nextstate:=snOnTreatment
end
else if tJR=tChange then
  nextstate:=snJointReplacement
else
  nextstate:=snQuitDMARD;
end;

procedure quitDMARD;
var x,x2,p,q,r:real;
begin
  if HAQshift>3-HAQcurrent then HAQshift:=3-HAQcurrent;
  x2:=linint(nThisDMARD,RAtoxmat,12,0,1);
  HAQcurrent:=HAQcurrent+HAQshift;
  x:=HAQshift*HAQ2QoLb;
  uTotAbsolute:=uTotAbsolute+tEndLoss*x;
  uTotDiscount:=uTotDiscount+tEndLoss*x*exp(-DiscRateUtils*tTotal);
  if x2=0 then
begin
  JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
  nextstate:=snSelectNextTreatment
end
else
begin
  p:=linint(nThisDMARD,RAtoxicity,12,0,1);
  q:=linint(nThisDMARD,RAtoxicity,12,0,2);
  r:=linint(nThisDMARD,RAtoxicity,12,0,3);
  x:=standarduniform;
  if x<p+q*exp(-r*tThisDMARD) then
begin
  zToxicity:=1;
  JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
  nextstate:=snSelectNextTreatment
end
else
begin
  JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
  nextstate:=snSelectNextTreatment
end
end;
end;

procedure selectnexttreatment;
begin
  if nDMARDsLeft<=1 then
begin
  nDMARDsLeft:=0;
  nThisDMARD:=0;

```

```

    nextstate:=snStartnewTreatment
end
else
begin
    nDMARDsLeft:=nDMARDsLeft-1;
    nThisDMARD:=round(linint(nDMARDsleft,RAStratList,11,0,aaStrategy));
    if nThisDMARD>11 then
    begin
        if zToxicity>0 then
            nextstate:=snSelectNextTreatment
        else
            nextstate:=snStartnewTreatment
        end
    else
        nextstate:=snStartnewTreatment;
    end
end;

procedure jointreplacement;
var x:real;
begin
    JRcount:=JRcount+1;
    cTotAbsolute:=cTotAbsolute+cJR;
    cTotDiscount:=cTotDiscount+cJR*exp(-DiscRateCosts*tTotal);
    x:=standarduniform;
    if x<pDeathJR then
    begin
        nextstate:=snDeath;
    end
    else
    begin
        JRcol:=2;
        JRRiska:=JRRiska2;
        tAtRiskJR:=0;
        x:=standarduniform;
        if x>pFailJR then
        begin
            HAQcurrent:=linint(HAQcurrent,RAHAQJR,24,0,1);
            JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
            nextstate:=snOnTreatment;
        end
        else
        begin
            x:=standarduniform;
            if x<pRepeatJR then
            begin
                JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
                nextstate:=snJointReplacement
            end
            else
            begin
                JRRiskb:=linint(HAQcurrent,RAJRb,24,0,JRcol);
                nextstate:=snOnTreatment;
            end
        end
    end
end;

procedure death;
{if the patient dies before reaching the point of divergence between}
{strategies, that patient is discarded and a new patient started}

```



```

begin
  if zDivReached=0 then
  begin
    rejects:=rejects+1;
    nextstate:=snstart
  end
  else
  begin
    nextstate:=snInclude
  end
end;

procedure include;
{count number of patients by last treatment}
{variable zDead used to cause loops to end}
begin
  lasttreatment [aastrategy, nThisDMARD] :=
    lasttreatment [aastrategy, nThisDMARD] +1;
  zDead:=1;
end;

procedure onestep;
{calls the appropriate procedure for the next single step}
begin
  case nextstate of
    snstart:newpatient;
    snStartnewTreatment:startnewtreatment;
    snOnTreatment:ontreatment;
    snQuitDMARD:quitDMARD;
    snSelectNextTreatment:selectnexttreatment;
    snJointReplacement:jointreplacement;
    snDeath:death;
    snInclude:include;
  end;
end;

procedure fulllife;
{runs the full life for a single patient}
begin
  newpatient;
  repeat
    onestep
  until zDead=1;
end;

procedure fullsample;
{runs a full sample for a single strategy}
var s:string;
    n,n1,n2,i,j1,j2:integer;
    x,nx,tca,tcasq,tcd,tcdsq,tua,tuasq,tud,tudsq:real;
begin
  {first initialise counters}
  callstoRNG:=0;
  JRcount:=0;
  rejects:=0;
  {if fixed seed required, then use it}
  {seed must be strictly between 0 and 1 or it will be ignored}
  if Form1.CheckBox2.Checked then
  begin
    s:=Form1.Edit5.Text;
    val(s,x,i);
    if ((x>0) and (x<1)) then ranseeds:=trunc(x*RanM);
  end;
end;

```

```

{find sample size from edit box}
s:=Form1.Edit2.Text;
val(s,n,i);
{to ensure that screen display is updated frequently}
{during the run, the running loop is split into an}
{inner and an outer loop}
{the inner loop is completed every 1000 patients}
{and updated totals are displayed}
if n>1000 then n2:=1000 else n2:=n;
n1:=(n+n2-1) div n2;
{set sample totals to 0}
tca:=0;
tcasq:=0;
tcd:=0;
tcdsq:=0;
tua:=0;
tuasq:=0;
tud:=0;
tudsq:=0;
s:=Form1.Edit1.Text;
val(s,aaStrategy,i);
for i:=0 to 12 do
  lasttreatment[aaStrategy,i]:=0;
{run in blocks of 1000}
for j1:=1 to n1 do
begin
  for j2:=1 to n2 do
    {for each patient in block, run full life then update totals}
    begin
      fulllife;
      {this condition should now be redundant}
      if zDivReached>0 then
        begin
          tca:=tca+cTotAbsolute;
          tcasq:=tcasq+cTotAbsolute*cTotAbsolute;
          tcd:=tcd+cTotDiscount;
          tcdsq:=tcdsq+cTotDiscount*cTotDiscount;
          tua:=tua+uTotAbsolute;
          tuasq:=tuasq+uTotAbsolute*uTotAbsolute;
          tud:=tud+uTotDiscount;
          tudsq:=tudsq+uTotDiscount*uTotDiscount;
        end
      end;
    {calculate means and standard errors to display}
    {this shows progress but it is not designed to allow interruption}
    nx:=j1*n2;
    Form1.ListBox1.Clear;
    s:='After '+InttoStr(trunc(nx))+ ' cases';
    Form1.ListBox1.Items.Add(s);
    s:='Discounted Cost';
    Form1.ListBox1.Items.Add(s);
    thiscmean:=tcd/nx;
    s:=format(' mean %10.2f', [thiscmean]);
    Form1.ListBox1.Items.Add(s);
    x:=(tcdsq*nx-tcd*tcd)/(nx*nx);
    thiscse:=sqrt(x/nx);
    s:=format(' S.E. %10.2f', [thiscse]);
    Form1.ListBox1.Items.Add(s);
    s:='Discounted Utility';
    Form1.ListBox1.Items.Add(s);
    thisumean:=tud/nx;
    s:=format(' mean %10.4f', [thisumean]);

```

```

Form1.ListBox1.Items.Add(s);
x:=(tudsq*nx-tud*tud)/(nx*nx);
thisuse:=sqrt(x/nx);
s:=format(' S.E. %10.4f',[thisuse]);
Form1.ListBox1.Items.Add(s);
s:=' ';
Form1.ListBox1.Items.Add(s);
for i:=0 to 12 do
begin
  nx:=lasttreatment[aaStrategy,i];
  if nx>0 then
  begin
    s:=' '+DMARDnames[i]+format(' %8d',[trunc(nx)]);
    Form1.ListBox1.Items.Add(s);
  end
end;
Form1.ListBox1.Refresh;
end;
{show various other totals at end of run}
{if number of calls to RNG exceeds 9 figures,}
{need a RNG with longer cycle}
s:=' ';
Form1.ListBox1.Items.Add(s);
s:=inttostr(callstoRNG)+' calls to RNG';
Form1.ListBox1.Items.Add(s);
{if there are any timing errors, then debugging is needed}
s:=inttostr(negchange)+' timing errors';
{this shows the number of patients who did not reach}
{the point of divergence between the strategies}
Form1.ListBox1.Items.Add(s);
s:=inttostr(rejects)+' patients discarded';
Form1.ListBox1.Items.Add(s);
s:=inttostr(JRcount)+' joint replacements';
Form1.ListBox1.Items.Add(s);
Form1.Button4.Enabled:=false;
end;

procedure TForm1.Button1Click(Sender: TObject);
{Exit the Program}
begin
  close
end;

procedure TForm1.Button2Click(Sender: TObject);
{Initialise and input data}
begin
  readandinit
end;

procedure TForm1.Button3Click(Sender: TObject);
{New patient - enables Advance one step and restart this patient}
begin
  newpatient;
  showtrackers;
  Button4.Enabled:=true;
  Button7.Enabled:=true;
end;

procedure TForm1.Button4Click(Sender: TObject);
{Advance one step}
begin
  onestep;

```

```
    showtrackers;
    if zDead=1 then Button4.Enabled:=false;
end;

procedure TForm1.Button5Click(Sender: TObject);
{Complete patient life}
begin
    fulllife;
    showtrackers;
    Button4.Enabled:=false;
end;

procedure TForm1.Button6Click(Sender: TObject);
{Full run}
begin
    fullsample;
end;

procedure TForm1.Button7Click(Sender: TObject);
{Restart same patient}
begin
    ranseeds:=storedseed;
    newpatient;
    showtrackers;
    Button4.Enabled:=true;
end;

procedure TForm1.Button8Click(Sender: TObject);
{Strategies}
{can run any set of consecutively numbered strategies}
var st0,st1,st2,st9,i:integer;
    x,x1,x2,nx,px:real;
    s,s1:string;
begin
    {read strategy numbers}
    s:=Edit3.text;
    val(s,x,i);
    st1:=trunc(x);
    s:=Edit4.text;
    val(s,x,i);
    st2:=trunc(x);
    {reverse order of ends if necessary}
    if st2<st1 then
    begin
        st0:=st1;
        st1:=st2;
        st2:=st0
    end;
    {go through each strategy in turn}
    for st0:=st1 to st2 do
    begin
        {set strategy number in text box and refresh display}
        Edit1.text:=inttostr(st0);
        Edit1.refresh;
        fullsample;
        {preserve totals and standard errors}
        allcmean[st0]:=thiscmean;
        allcse[st0]:=thiscse;
        allumean[st0]:=thisumean;
        alluse[st0]:=thisuse;
    end;
    {display results for each strategy in turn}
```

```

ListBox1.Clear;
for st0:=st1 to st2 do
begin
  s1:='Strategy '+inttostr(st0);
  s:=s1+' - Cost';
  Form1.ListBox1.Items.Add(s);
  thiscmean:=allcmean[st0];
  s:=format(' mean %10.2f', [thiscmean]);
  Form1.ListBox1.Items.Add(s);
  thiscse:=allcse[st0];
  s:=format(' S.E. %10.2f', [thiscse]);
  Form1.ListBox1.Items.Add(s);
  s:=s1+' - Utility';
  Form1.ListBox1.Items.Add(s);
  thisumean:=allumean[st0];
  s:=format(' mean %10.3f', [thisumean]);
  Form1.ListBox1.Items.Add(s);
  thisuse:=alluse[st0];
  s:=format(' S.E. %10.4f', [thisuse]);
  Form1.ListBox1.Items.Add(s);
  s:=' ';
  Form1.ListBox1.Items.Add(s);
  nx:=0;
  for i:=0 to 12 do
  begin
    nx:=nx+lasttreatment[st0,i];
  end;
  for i:=0 to 12 do
  begin
    px:=100*lasttreatment[st0,i]/nx;
    if px>0 then
    begin
      s:=' '+DMARDnames[i]+format(' %6.1f', [px]);
      Form1.ListBox1.Items.Add(s);
    end
  end;
  s:=' ';
  Form1.ListBox1.Items.Add(s);
end;
for st0:=st1 to st2-1 do
begin
  for st9:=st0+1 to st2 do
  begin
    s1:='Strategy '+inttostr(st0)+' - Strategy '+inttostr(st9);
    s:=' ';
    Form1.ListBox1.Items.Add(s);
    Form1.ListBox1.Items.Add(s1);
    s:='Cost';
    Form1.ListBox1.Items.Add(s);
    thiscmean:=allcmean[st0]-allcmean[st9];
    s:=format(' mean %10.2f', [thiscmean]);
    Form1.ListBox1.Items.Add(s);
    x:=allcse[st0]*allcse[st0]+allcse[st9]*allcse[st9];
    thiscse:=sqrt(x);
    s:=format(' S.E. %10.2f', [thiscse]);
    Form1.ListBox1.Items.Add(s);
    s:='Utility';
    Form1.ListBox1.Items.Add(s);
    thisumean:=allumean[st0]-allumean[st9];
    s:=format(' mean %10.3f', [thisumean]);
    Form1.ListBox1.Items.Add(s);
    x:=alluse[st0]*alluse[st0]+alluse[st9]*alluse[st9];

```

```
thisuse:=sqrt(x);
s:=format(' S.E. %10.4f', [thisuse]);
Form1.ListBox1.Items.Add(s);
x:=thiscmean/thisumean;
if x>0 then
begin
  s:=' ICER';
  Form1.ListBox1.Items.Add(s);
  s:=format(' point %10d', [round(x)]);
  x1:=1/x;
  x2:=sqrt((thisuse*thisuse)/(thiscmean*thiscmean)
    +(thisumean*thisumean*thiscse*thiscse)
    /(thiscmean*thiscmean*thiscmean*thiscmean));
  x:=1/(x1+x2+x2);
  Form1.ListBox1.Items.Add(s);
  s:=format(' lower %10d', [round(x)]);
  x:=1/(x1-x2-x2);
  Form1.ListBox1.Items.Add(s);
  s:=format(' upper %10d', [round(x)]);
end
else
  s:=' dominance';
  Form1.ListBox1.Items.Add(s);
end
end
end;

end.
```

## Appendix 5

### Sampling from conditional distributions

#### Survival distribution

Survival calculations are based on the life tables shown in *Table 36*. These were derived from 'normal actuarial age/sex specific death rates' used in the original Wyeth etanercept model.

For example, the general population probability for a female of surviving to at least the age of 60 is 0.9242, and to the age of 80 is 0.5822. Then, the conditional probability that a woman drawn from the general population who has reached the age of 60 will survive for at least another 20 years is  $\frac{0.5822}{0.9242} = 0.6300$ . For RA patients, there is an

increased risk of mortality dependent on HAQ score. This is modelled as a hazard ratio. Standard risk analysis tells us that the conditional probability is taken to the power of the hazard ratio. Thus, the probability that a woman with RA at a hazard ratio of 1.5 who has reached the age of 60 will survive for at least another 20 years is  $\left(\frac{0.5822}{0.9242}\right)^{1.5} = 0.5000$ . Generalising, consider an

RA patient of age  $x$  with hazard ratio  $r$ , and suppose that it is desired to find the probability  $p$  of survival to age  $y$ . Let  $a$  and  $b$  be the gender-specific survival probabilities for ages  $x$  and  $y$ , respectively, for a member of the general population. Then,  $p = \left(\frac{b}{a}\right)^r$ . This equation may

be rearranged to give  $b = a(p^{1/r})$ . This gives the method for sampling from a conditional distribution on age. Consider the case of a 60-year-old woman with RA at hazard ratio 1.5 and suppose that the random number drawn is

0.5000. From the life tables, the general population survival probability at the age of 60 is 0.9242. Multiplying by  $0.5000^{1/1.5}$  we obtain 0.5822. The tables are then used in inverse form to find the age at death, in this case 80 years.

#### Weibull distributions

For conditional sampling from Weibull distributions, an alternative method is more convenient. As noted earlier, if  $X$  has a Weibull distribution with parameters  $a$  and  $b$ , then  $\left(\frac{X}{b}\right)^a$

has an exponential distribution with unit mean. The exponential distribution has the property that the conditional distribution of time to event remains constant as long as no event has occurred. When sampling time to quit a DMARD (in the 'Resume DMARD' event joint replacement (at the start of the 'On treatment' activity), let  $t$  be the time already spent on the DMARD at risk of joint replacement, and let  $u$  be a value sampled from an exponential distribution with unit mean. Then, the required time to event is  $v$ , where

$\left(\frac{t}{b}\right)^a + u = \left(\frac{t+v}{b}\right)^a = w$ , say. First calculating

$w = \left(\frac{t}{b}\right)^a + u$ , we then have  $v = b(w^{1/a}) - t$ . The

same method is used to calculate the time to joint replacement in terms of the time spent at risk of joint replacement. The time spent at risk of joint replacement is initially zero, and is returned to zero every time a new joint replacement occurs. However, the parameters of the Weibull distribution change when the joint replacement is made.

TABLE 36 Life tables used in the BRAM

Age	Male	Female	Age	Male	Female
0	1	1	51	0.9400	0.9626
1	0.9936	0.9949	52	0.9358	0.9597
2	0.9931	0.9945	53	0.9311	0.9566
3	0.9928	0.9942	54	0.9258	0.9532
4	0.9926	0.9941	55	0.9198	0.9494
5	0.9924	0.9940	56	0.9134	0.9452
6	0.9923	0.9938	57	0.9063	0.9408
7	0.9921	0.9937	58	0.8981	0.9357
8	0.9920	0.9936	59	0.8894	0.9302
9	0.9918	0.9935	60	0.8800	0.9242
10	0.9917	0.9934	61	0.8696	0.9175
11	0.9916	0.9933	62	0.8582	0.9102
12	0.9914	0.9932	63	0.8459	0.9022
13	0.9913	0.9931	64	0.8323	0.8937
14	0.9911	0.9929	65	0.8175	0.8842
15	0.9908	0.9928	66	0.8010	0.8737
16	0.9906	0.9926	67	0.7834	0.8622
17	0.9901	0.9923	68	0.7639	0.8495
18	0.9896	0.9920	69	0.7432	0.8359
19	0.9888	0.9917	70	0.7206	0.8208
20	0.9880	0.9914	71	0.6961	0.8041
21	0.9871	0.9911	72	0.6699	0.7858
22	0.9863	0.9908	73	0.6422	0.7657
23	0.9854	0.9905	74	0.6129	0.7441
24	0.9845	0.9902	75	0.5818	0.7210
25	0.9836	0.9898	76	0.5498	0.6966
26	0.9827	0.9895	77	0.5163	0.6701
27	0.9819	0.9892	78	0.4825	0.6426
28	0.9810	0.9888	79	0.4478	0.6130
29	0.9801	0.9885	80	0.4122	0.5822
30	0.9791	0.9880	81	0.3763	0.5489
31	0.9782	0.9876	82	0.3407	0.5144
32	0.9773	0.9871	83	0.3052	0.4782
33	0.9762	0.9867	84	0.2701	0.4411
34	0.9752	0.9861	85	0.2364	0.4030
35	0.9741	0.9856	86	0.2042	0.3640
36	0.9731	0.9849	87	0.1743	0.3248
37	0.9719	0.9842	88	0.1465	0.2864
38	0.9707	0.9835	89	0.1213	0.2493
39	0.9694	0.9826	90	0.0988	0.2139
40	0.9680	0.9817	91	0.0794	0.1816
41	0.9664	0.9807	92	0.0634	0.1526
42	0.9647	0.9796	93	0.0497	0.1258
43	0.9628	0.9783	94	0.0383	0.1018
44	0.9607	0.9769	95	0.0289	0.0806
45	0.9584	0.9753	96	0.0213	0.0625
46	0.9559	0.9736	97	0.0155	0.0472
47	0.9533	0.9719	98	0.0108	0.0348
48	0.9503	0.9698	99	0.0074	0.0251
49	0.9471	0.9676	100	0.0050	0.0177
50	0.9437	0.9652	101	0	0



## Appendix 6

# Details of published data about HAQ changes for DMARDs

### Azathioprine

- Azathioprine HAQ: none of the trials in the Cochrane library (azathioprine versus placebo, three trials including a grand total of 33 patients treated with effective doses of azathioprine) gives HAQ data.<sup>62</sup>
- Only one of the studies, of azathioprine against other DMARDs,<sup>63-67</sup> appears to have HAQ data, but the azathioprine group in this study only had 27 patients.<sup>67</sup> The patients appeared to be a group with severe disease (baseline HAQ scores of 1.8). Change in HAQ at 6 months was recorded at 0.1 for azathioprine and for ciclosporin groups.
- This is not sufficiently robust for the present modelling purposes.
- The head-to-head studies appear to suggest that azathioprine is similar to ciclosporin in efficacy, but less good than methotrexate (in some studies). Therefore, it could be assumed that efficacy is similar to ciclosporin in terms of HAQ, especially as the two agents are likely to be used in similar sorts of patient. See below for ciclosporin comments and for data to use for azathioprine.

### Ciclosporin A (CyA)

- Ciclosporin A HAQ: none of the placebo-controlled trials in the Cochrane database used HAQ as an outcome.
- However, comparative trials and observations studies show:
  - HAQ score changes by 0.34 at 24 weeks and by 0.5 (compared with baseline) after 52 weeks of treatment in a trial of ciclosporin (two different preparations).<sup>68</sup> This HAQ data should be assumed to apply to azathioprine also (see above). In this trial of 144 patients given CyA, 46 (32%) dropped out before 24 weeks, 35 (24.3%) because of adverse effects; 78 patients received a further 6 months and of these 24 (16.7%) dropped out.
  - A study of early RA patients<sup>69,70</sup> (mean disease duration 1 year) compared CyA and gold (177 patients CyA and 183 patients

gold). HAQ at 'study end-point', i.e. when withdrawn or after 18 months [intention-to-treat (ITT) analysis] declined by 0.4 (from a baseline of 1.1) in both groups. These were early RA patients and since CyA is not generally used early these data are not useful for the present model.

- Other studies provide HAQ, or related, data; for example, Altman and colleagues measured mHAQ.<sup>71</sup> Altman's group did not see any changes in mHAQ other than in some subcategories when they tested CyA against placebo.
- Another recent study of CyA, sulfasalazine and methotrexate did not provide HAQ data.<sup>72</sup>

### Etanercept and infliximab

The data used in the original model<sup>2</sup> are the most robust available as they are based on an up-to-date systematic review. Therefore, this is the appropriate patient population and HAQ changes of 0.6 over the study duration are appropriate. It appears that the maximal change in HAQ is achieved over 6 months and then stabilises.

### Gold (GST)

Median HAQs in a cohort from Glasgow<sup>73</sup> are shown in *Table 37* (data appear to be from patients who completed 5 years on gold).

The middle and bottom rows of patients are most likely to represent the population in the model, since gold appears to be third or fourth choice for most UK rheumatologists. Therefore, it is likely that at least 2 years will have elapsed before gold is used.

### Hydroxychloroquine (HCQ)

As the survey indicates, HCQ is likely to be used early in disease in some cases or added to methotrexate where there is a suboptimal response. However, for modelling these two approaches

**TABLE 37** Median HAQs in a cohort from Glasgow

Disease duration when starting drug	Year 0	Year 1	Change at 1 year	Year 2	Year 3	Year 4	Year 5
0–2 years (n = 44)	1.88	1.06	0.82	1	1	1.13	1.25
2–5 years (n = 37)	1.75	1.13	0.62	1.25	1.27	1.57	1.81
> 5 years (n = 79)	2.00	1.57	0.43	1.5	1.75	1.75	2.13

**TABLE 38** Changes in HAQ scores using data from leflunomide trials

	Leflunomide		Sulfasalazine		Methotrexate	
	ITT group (n = 802)	6-month completers (n = 621)	ITT group (n = 132)	6-month completers (n = 86)	ITT group (n = 669)	6-month completers (n = 547)
Mean HAQ change at 1 month	–0.21	–0.22	–0.09	–0.15	–0.11	–0.12
Mean HAQ change at 6 months	–0.38	–0.45	–0.29	–0.43	–0.34	–0.40

should be considered. Three recent trials of HCQ were assessed to gauge the effect on HAQ. In one trial against minocycline the HAQ changed from 1.32 to 0.74 (difference 0.58) over a 2-year period (ITT).<sup>74</sup> Another recent dose-loading study used mHAQ, which does not suit the present purposes.<sup>75</sup> At the time of writing, details could not be obtained for the HERA study.<sup>76</sup>

### Leflunomide (LEF)

Changes in HAQ scores, using data from leflunomide trials,<sup>77</sup> are shown in *Table 38*.

These data make clinical sense. Although it would make more sense to use the data relating to

6-month completers in a model that tries to reflect clinical practice, ITT data had to be used for other DMARDs. Thus, ITT data from the above summary for leflunomide, methotrexate and sulfasalazine were used for consistency.

### Methotrexate and sulfasalazine (MTX and SSZ)

See the above paragraph for the source of estimates.<sup>77</sup> Using data from a similar population means that data are drawn from a similar population base, but note that, for other DMARDs, data were drawn from different studies using different populations and different practices.

## Appendix 7

### Health Assessment Questionnaire (HAQ)<sup>33</sup>

<b>Patient Label</b>		<b>Date:</b>		
We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments at the end of this form.				
<b>PLEASE TICK THE ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK</b>				
	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
	Score = 0	Score = 1	Score = 2	Score = 3
<b>1. DRESSING &amp; GROOMING – Are you able to:</b>				
– Dress yourself including tying shoelaces and doing buttons?				
– Shampoo your hair?				
<b>2. RISING – Are you able to:</b>				
– Stand up from an armless straight chair?				
– Get in and out of bed?				
<b>3. EATING – Are you able to:</b>				
– Cut your meat?				
– Lift a cup or glass to your mouth?				
– Open a new carton of milk (or soap powder)?				
<b>4. WALKING – Are you able to:</b>				
– Walk outdoors on flat ground?				
– Climb up five steps?				

<b>PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES</b>			
Cane		Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)	
Walking frame		Built-up or special utensils	
Crutches		Special or built-up chair	
Wheelchair		Other (specify)	

<b>PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON</b>			
Dressing and grooming		Eating	
Rising		Walking	

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	Unable to do
	Score = 0	Score = 1	Score = 2	Score = 3
<b>5. HYGIENE – Are you able to</b> – Wash and dry your entire body? – Take a bath? – Get on and off the toilet?				
<b>6. REACH – Are you able to</b> – Reach and get a 5 lb object (e.g. a bag of potatoes) from above your head)? – Bend down to pick up clothing from the floor?				
<b>7. GRIP – Are you able to</b> – Open car doors? – Open jars which have been previously opened? – Turn taps on and off?				
<b>8. ACTIVITIES – Are you able to</b> Run errands and shop? Get in and out of a car? Do chores such as vacuuming, housework or light gardening?				

**PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:**

Raised toilet seat		Jar opener (for jars previously opened)	
Bath seat		Long handled appliances for reach	
Bath rail		Other (specify)	

**PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON**

Hygiene		Gripping and opening things	
Reach		Errands and housework	

## Scoring of HAQ

Add the maximum score for each of the 8 sections and divide by 8 to give a score between 0 to 3. If aid/device or help is needed the score for that activity automatically = 2 (unless 3 has already been ticked).

Normal function = 0, Most severely affected = 3.

## Appendix 8

### ACR classification of functional status in RA

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)	Usual self-care means dressing, feeding, bathing, grooming and toileting.
Class II	Able to perform usual self-care and vocational activities but limited in avocational activities	Avocational means recreational and/or leisure activities.
Class III	Able to perform usual self-care activities but limited in vocational and avocational activities	Vocational means work, school and homemaking. Both of the latter are specific to individuals and age and gender specific.
Class IV	Limited ability to perform usual self-care, vocational and avocational activities	



## Appendix 9

### Regression analysis of QoL against HAQ

Nigel Hurst kindly made available the data set reported in Hurst and colleagues.<sup>30</sup>

The data set consists of patient-level data for 233 patients, drawn in approximately equal numbers from the four functional classes of RA. Variables included in the data set included functional class, age, gender, years of education, years with arthritis, RF and presence or absence of swollen joints, as well as HAQ and EQ-5D. The EQ-5D responses were recorded as the answers to the five separate dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression), together with the utility derived from these and the visual analogue scale ('thermometer') score. From the modelling point of view, the aim was to predict QoL as a function of other variables in the model. Thus, it seemed sensible to work with utility as a function of HAQ, gender and age.

Table 39 shows the result of a regression of utility against the three variables indicated.

As can be seen in Table 39, neither gender nor age contributed significantly to the regression analysis.

**TABLE 39** Utility versus gender, age, HAQ

	Coefficients	SE	t-Statistic	p-Value
Intercept	0.807	0.0807	10.00	< 0.001
Gender	0.00835	0.0425	0.196	0.845
Age	0.00100	0.00127	0.790	0.430
HAQ	-0.335	0.0224	-15.0	< 0.001

**TABLE 40** Utility versus age, HAQ

	Coefficients	SE	t-Statistic	p-Value
Intercept	0.816	0.0659	12.4	< 0.001
Age	0.00103	0.00126	0.813	0.417
HAQ	-0.335	0.0223	-15.06	< 0.001

Removing gender gave the analysis shown in Table 40.

The variable age was still not a significant predictor of utility, so it was dropped. This led to Table 41.

This regression analysis has an  $R^2$  value of 0.539, suggesting that just over half of the variance in utility can be explained by a linear relationship with HAQ. However, it is possible that a better fit can be obtained from a non-linear relationship. Tables 42 and 43 show results of incorporating squares and cubes of HAQ. From these, it is clear that the linear relationship indicated in Table 41 is the most appropriate.

**TABLE 41** Utility versus HAQ

	Coefficients	SE	t-Statistic	p-Value
Intercept	0.862	0.0340	25.3	< 0.001
HAQ	-0.327	0.0201	-16.3	< 0.001

**TABLE 42** Utility versus HAQ, HAQ<sup>2</sup>

	Coefficients	SE	t-Statistic	p-Value
Intercept	0.805	0.0477	16.9	< 0.001
HAQ	-0.203	0.0759	-2.67	0.008
HAQ <sup>2</sup>	-0.0444	0.0261	-1.70	0.091

**TABLE 43** Utility versus HAQ, HAQ<sup>2</sup>, HAQ<sup>3</sup>

	Coefficients	SE	t-Statistic	p-Value
Intercept	0.832	0.0585	14.2	< 0.001
HAQ	-0.327	0.175	-1.87	0.062
HAQ <sup>2</sup>	0.0650	0.141	0.461	0.645
HAQ <sup>3</sup>	-0.0254	0.0322	-0.790	0.430





## Appendix 10

### Rapid review of effect of joint replacement on HAQ

Ovid Technologies, Inc. Email Service

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Search for: from 4 [from 3 keep 12-13,20-21] keep 1-4

Citations: 1-4

Database: Medline <1966 to present>

Search Strategy: Both Embase & Medline used for strategy below

-----  
1 exp \*Joint Prosthesis/ (17089)

2 exp \*Quality of Life/ (13801)

3 1 and 2 (29)

4 from 3 keep 12-13, 20-21 (4)

5 exp Quality of Life/ (32492)

6 1 and 2 (29)

7 6 not 3 (0)

8 from 4 keep 1-4 (4)

9 from 4 keep 1-4 (4)

Norman-Taylor FH, Palmer CR, Villar RN  
(Addenbrooke's Hospital NHS Trust and the University of Cambridge, England).

Quality-of-life improvement compared after hip and knee replacement. *J Bone Joint Surg Br* 1996; **78**:74-7.

#### Abstract

Total hip and total knee arthroplasty both provide a considerable improvement in quality of life, but there is no evidence to suggest that one is more successful than the other. We studied 72 patients in a prospective trial before and after total hip or total knee replacement. We recorded scores for disability and distress derived from the Harris hip score and the British Orthopaedic Association knee assessment score, and used them to generate quality of life (QoL) scores using the Rosser Index Matrix immediately before and at one year after surgery. The patients awaiting knee replacement had significantly lower QoL scores than those awaiting hip replacement ( $p = 0.011$ ). The QoL scores at one year were high and almost identical for both groups ( $p = 0.46$ ). Further analysis showed that gender and weight were not significant predictors of improvement of QoL scores, but age ( $p = 0.03$ ) and whether the hip or knee was replaced ( $p = 0.006$ ) were significant factors.

Towheed TE, Hochberg MC. Health-related quality of life after total hip replacement [review]. *Semin Arthritis Rheum* 1996;**26**:483-91.

#### Abstract

Total hip replacement (THR) is a commonly performed orthopedic procedure with an increasing rate of utilization. It is performed to relieve symptoms of pain and help restore the loss of function that follows advanced hip diseases, including osteoarthritis, rheumatoid arthritis, and avascular necrosis. Although there are numerous studies evaluating patient outcomes after THR with respect to physical functioning and pain relief, relatively few studies have specifically evaluated changes in health-related quality of life (QoL). We reviewed a total of 20 studies that evaluated changes in QoL after THR. Results of all studies were consistent in showing beneficial and often dramatic improvements in QoL after elective THR. These improvements were most likely to occur within the first 3 to 6 months after THR. Future research should assess the impact of both patient-level predictors and the role of various surgical approaches in contributing to successful outcomes after THR.

Pitson D, Bhaskaran V, Bond H, Yarnold R, Drewett R. Effectiveness of knee replacement surgery in arthritis. *Int J Nurs Stud* 1994;**31**:49-56.

#### Abstract

This study examined the effectiveness of knee replacement surgery in an elderly population suffering from arthritis. Four questionnaires which measured pain, mobility, anxiety, depression and social isolation were completed by the study group before and after surgery to assess changes in physical function, psychological state, social interaction and somatic sensation. A statistically significant difference was found in pain which was reduced from a median score of 3 before the operation to 0 afterwards on an intensity scale of 0-5. Statistically significant improvements were also found in the mobility/dependency scores and in the level of anxiety and depression following the operation. It was concluded that knee replacement is a highly effective treatment for arthritis of the

knee, reducing pain, increasing mobility and improving the person's emotional state, thus improving the quality of life of the recipient. The use of separate questionnaires to measure single dimensions of quality of life as opposed to a single health profile is also discussed.

Katz JN, Phillips CB, Fossel AH, Liang MH. Stability and responsiveness of utility measures. *Med Care* 1994;**32**:183–8.

#### Abstract

No abstract available.

Tsuboi S, Nagaya I, Asai T, Iwata H (Department of Orthopedic Surgery, Nagoya National Hospital, Nakaku, Nagoya, Japan). Physical and psychosocial changes of rheumatoid arthritis patients who underwent lower limb joint replacement. *Jpn J Rheumatol* 1996;**6**:321–32.

#### Abstract

A continuous 5-year follow-up study of quality of life (QoL) was conducted on 79 rheumatoid arthritis patients who underwent total joint replacement (operated group) of major lower limb joints (knee or hip joint) at a single rheumatology department (hospital). A similar 5-year comparative study was also made of 20 rheumatoid arthritis patients with bone destruction of major lower limb joints who suffered pain but had not undergone joint replacement (non-operated group). The QoL was evaluated using the Sickness Impact Profile and the scores were calculated. The scores of the operated group showed a marked improvement ( $P < 0.01$ ), primarily in a physical sense, at 1 year postoperatively. At 5 years postoperatively as well, the scores of the operated group [excluding 10 patients (13%) who died] continued to show a significant improvement over the joint replacement levels in terms of overall score ( $P < 0.05$ ), physical score ( $P < 0.05$ ) and psychosocial score ( $P < 0.05$ ). Although the psychosocial score displayed no significant improvement up until the fourth year following initial operation, it did so thereafter. The scores of the non-operated group, on the other hand, showed the same level, worse and no improvement, in relation to the levels at the time the observation had begun. In the operated group, the postoperative QoL scores in each category showed little correlation with age, duration of disease or erythrocyte sedimentation rate, but a close correlation was found with the presence/absence of complications, number of joints and the scores before initial operation. The investigation revealed that, following the initial joint

replacement, the QoL in some rheumatoid arthritis patients declined either due to death or progressive physical dysfunction; however, in the majority of the patients, the QoL obviously improved up to 5 years not only physically but psychosocially.

Borstlap M, Zant JL, Van Soesbergen RM, Van Der Korst JK (Jan van Breemen Institute, Amsterdam, The Netherlands). Quality of life assessment: a comparison of four questionnaires for measuring improvements after total hip replacement. *Clin Rheumatol* 1995;**14**:15–20.

#### Abstract

Three experimental questionnaires were compared with the Influence of Rheumatic Diseases on Health and Lifestyle (IRGL) questionnaire, a Dutch version of the Arthritis Impact Measurement Scales. Sixty-two patients with osteoarthritis (OA) and 35 patients with rheumatoid arthritis (RA), all of whom underwent hip arthroplasty, completed the study. Results showed that visual analogue scales for pain, stiffness, fatigue, and anxiety were strongly correlated with a number of the IRGL scales. Patient preference scales were sensitive to change and provided additional information on aspects of the patients' quality of life (QoL) that were felt to be important by the patients themselves. The questionnaire on performance in various roles in life was insensitive to change. In existing questionnaires, there is an attempt to represent the concept of QoL in terms of its most important aspects. Such realizations of the concept of QoL are not entirely suitable for application in clinical trials. The IRGL is overly complex, and its sometimes comprehensive scales do not deal with the possible effects of treatment. Neither of these properties is conducive to sensitivity to change. Visual analogue scales reduce the complexity. A simpler representation of QoL that can evaluate aspects relevant to treatment is recommended.

Borstlap M, Zant JL, Van Soesbergen M, Van Der Korst JK (Jan van Breemen Instituut, Amsterdam The Netherlands). Effects of total hip replacement on quality of life in patients with osteoarthritis and in patients with rheumatoid arthritis. *Clin Rheumatol* 1994;**13**:45–50.

#### Abstract

The effects of total hip replacement (THR) on quality of life were investigated in 62 patients with osteoarthritis (OA) and 35 patients with rheumatoid arthritis (RA). Patients eligible for a first hip joint

replacement were enrolled consecutively and examined at home before the operation and 3, 6, and 12 months after surgery. The IRGL (Influence of Rheumatic Diseases on Health and Lifestyle), a Dutch version of the AIMS (Arthritis Impact Measurement Scales), was used to operationalize quality of life in a questionnaire. Pain and mobility scores showed significant improvement among both OA and RA patients. The general mood of the OA patients also improved significantly, but the RA group showed only a favourable tendency in this respect. The interference of OA in several areas of life almost disappeared, whereas the impact of RA was only slightly reduced. There was no discernible effect on the social dimension in either group. A single THR apparently solves the main problem of most OA patients, but only one of a number of joint problems for most RA patients. The IRGL is complex and time-consuming and contains irrelevant scales. Its multidimensional evaluation of the quality of life is more informative than a purely somatic evaluation.

Cleary PD, Reilly DT, Greenfield S, Mulley AG, Wexler L, Frankel F, McNeil BJ. Using patient reports to assess health-related quality of life after total hip replacement. *Qual Life Res* 1993;2:3-11.

#### **Abstract**

Data on disease severity, co-morbidity, and process of care were obtained from the medical records of 356 patient without rheumatoid arthritis undergoing a first unilateral total hip replacement at four teaching hospitals in California and Massachusetts. Socio-demographic characteristics, functional status prior and subsequent to hospitalization, and improvement in health status were measured with a patient questionnaire 12 months after discharge. Completed questionnaires were received from 284 patients, a response rate of 79.8%. The questionnaire was acceptable to patients, reliable, and had good construct validity. The data indicate substantial benefits from hip arthroplasty. As expected, pre-surgical functioning was a strong predictor of outcomes 1 year after surgery. Controlling for pre-surgical functioning, age was not related to outcomes.



# Appendix I I

## BRAM simulation model results

Tables 44–57 show simulation results for 1,000,000 virtual patients in each arm.

**TABLE 44** Base-case results for the BRAM (without joint replacement)

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	41,237	17.26	8.315	0.0052	46.3
Infliximab	34,925	14.34	8.090	0.0051	50.2
Base	15,953	5.22	7.814	0.0051	55.8

**TABLE 45** Results including joint replacement at £5000 (assumption)

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	42,490	17.75	9.274	0.0058	46.8
Infliximab	36,190	14.85	9.080	0.0058	50.7
Base	17,233	6.35	8.848	0.0058	56.3

**TABLE 46** Results for comparison anti-TNFs versus placebo

Strategy	Cost/patient (£)		QALYs/patient	
	Mean	q.s.e.	Mean	q.s.e.
Etanercept	32,316	17.53	7.524	0.0048
Infliximab	24,580	14.32	7.217	0.0048
Base	3,250	1.41	6.836	0.0048

**TABLE 47** Results for comparison using new strategy 1

Strategy	Cost/patient (£)		QALYs/patient	
	Mean	q.s.e.	Mean	q.s.e.
Etanercept	40,474	17.32	8.228	0.0051
Infliximab	34,024	14.40	7.983	0.0050
Base	14,811	5.28	7.674	0.0050

**TABLE 48** Results for comparison using new strategy 2

Strategy	Cost/patient (£)		QALYs/patient	
	Mean	q.s.e.	Mean	q.s.e.
Etanercept	39,451	17.41	8.290	0.0051
Infliximab	32,854	14.50	8.059	0.0051
Base	13,457	5.59	7.776	0.0051

**TABLE 49** Results for comparison using new strategy 1 with anti-TNFs in fourth place

Strategy	Cost/patient (£)		QALYs/patient	
	Mean	q.s.e.	Mean	q.s.e.
Etanercept	39,531	17.38	7.179	0.0048
Infliximab	33,150	14.40	6.902	0.0047
Base	13,970	5.07	6.553	0.0047

**TABLE 50** Results for comparison using new strategy 2 with anti-TNFs in sixth place

Strategy	Cost/patient (£)		QALYs/patient	
	Mean	q.s.e.	Mean	q.s.e.
Etanercept	35,590	17.46	5.789	0.0043
Infliximab	29,051	14.41	5.501	0.0043
Base	9,350	4.56	5.126	0.0042

**TABLE 51** Results with minimum improvement for joint replacement

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	42,539	17.80	8.601	0.0053	46.4
Infliximab	36,261	14.92	8.380	0.0053	50.3
Base	17,315	6.50	8.119	0.0053	56.0

**TABLE 52** Results with maximum improvement in HAQ to zero

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	42,463	17.73	9.914	0.0064	47.2
Infliximab	36,137	14.80	9.740	0.0064	51.1
Base	17,176	6.26	9.523	0.0064	56.6

**TABLE 53** Result for the BRAM including offset costs

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	49,956	19.90	8.315	0.0052	46.3
Infliximab	44,004	17.20	8.090	0.0051	50.2
Base	25,653	10.62	7.814	0.0051	55.8

**TABLE 54** Results assuming that only anti-TNFs reduce the general deterioration in patient condition

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	41,291	17.29	8.655	0.0053	46.5
Infliximab	34,961	14.35	8.294	0.0052	50.3
Base	15,953	5.22	7.814	0.0051	55.8

**TABLE 55** Results assuming that all DMARDs reduce the general deterioration in patient condition

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	41,423	17.27	9.937	0.0059	47.8
Infliximab	35,088	14.35	9.661	0.0058	51.5
Base	16,070	5.21	9.313	0.0058	56.9

**TABLE 56** Results for a starting population of 15–25-year-old females

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	47,405	16.13	11.928	0.0062	90.5
Infliximab	39,951	13.55	11.644	0.0062	91.9
Base	19,794	3.65	11.330	0.0062	93.4

**TABLE 57** Results for a starting population of 75–85-year-old males

Strategy	Cost/patient (£)		QALYs/patient		% Ending on palliation
	Mean	q.s.e.	Mean	q.s.e.	
Etanercept	25,857	15.27	3.142	0.0024	3.0
Infliximab	23,396	12.83	3.009	0.0024	4.3
Base	8,710	3.90	2.811	0.0023	7.5







# Health Technology Assessment Programme

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## Diagnostic Technologies & Screening Panel

### Members

<p><b>Chair,</b> <b>Dr Ron Zimmern</b>, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge</p>	<p>Dr David Elliman, Consultant in Community Child Health, London</p> <p>Dr Andrew Farmer, Senior Lecturer in General Practice, Institute of Health Sciences, University of Oxford</p> <p>Dr Karen N Foster, Clinical Lecturer, Dept of General Practice &amp; Primary Care, University of Aberdeen</p> <p>Professor Jane Franklyn, Professor of Medicine, University of Birmingham</p> <p>Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust</p>	<p>Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London</p> <p>Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London</p> <p>Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton</p> <p>Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust</p> <p>Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust, Devon</p>	<p>Mr Tony Tester, Chief Officer, South Bedfordshire Community Health Council, Luton</p> <p>Dr Andrew Walker, Senior Lecturer in Health Economics, University of Glasgow</p> <p>Professor Martin J Whittle, Head of Division of Reproductive &amp; Child Health, University of Birmingham</p> <p>Dr Dennis Wright, Consultant Biochemist &amp; Clinical Director, Pathology &amp; The Kennedy Galton Centre, Northwick Park &amp; St Mark's Hospitals, Harrow</p>
<p>Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth</p> <p>Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge</p>			

## Pharmaceuticals Panel

### Members

<p><b>Chair,</b> <b>Dr John Reynolds</b>, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital</p> <p>Professor Tony Avery, Professor of Primary Health Care, University of Nottingham</p> <p>Professor Iain T Cameron, Professor of Obstetrics &amp; Gynaecology, University of Southampton</p> <p>Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London</p>	<p>Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre, Bushey, Herts.</p> <p>Mr Charles Dobson, Special Projects Adviser, Department of Health</p> <p>Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham</p> <p>Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff</p> <p>Professor Alastair Gray, Professor of Health Economics, University of Oxford</p>	<p>Mrs Sharon Hart, Managing Editor, <i>Drug &amp; Therapeutics Bulletin</i>, London</p> <p>Dr Christine Hine, Consultant in Public Health Medicine, Bristol South &amp; West Primary Care Trust</p> <p>Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton</p> <p>Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London</p> <p>Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool</p>	<p>Dr Ken Stein, Senior Lecturer in Public Health, University of Exeter</p> <p>Professor Terence Stephenson, Professor of Child Health, University of Nottingham</p> <p>Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry, London</p> <p>Professor Dame Jenifer Wilson-Barnett, Head of Florence Nightingale School of Nursing &amp; Midwifery, King's College, London</p>
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## Therapeutic Procedures Panel

### Members

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**Professor Bruce Campbell,**  
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Dr Mahmood Adil, Head of  
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Professor Norman Waugh,  
Professor of Public Health,  
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## Expert Advisory Network

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### Members

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Mr Gordon Aylward,  
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### **Feedback**

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (<http://www.ncchta.org>) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***