National Audit Office

Services for people with rheumatoid arthritis

ECONOMIC MODELS OF IDENTIFICATION AND TREATMENT OF EARLY RHEUMATOID ARTHRITIS

Principal authors: David Xu, Chris Groom, National Audit Office. Dr Matthew Taylor, York Health Economics Consortium was commissioned to provide validation and assurance about the quality of the models.

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Stephen Bevan, Managing Director, the Work Foundation;
Sarah Byford, Analyst, York Health Economics Consortium;
Elizabeth Camacho, Research Assistant, NOAR, ARC Epidemiology Unit, University of Manchester;
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Dr Patrick Kiely, Consultant Rheumatologist, St George's Hospital;
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Professor Deborah Symmons, Consultant Rheumatologist, East Cheshire NHS trust/Director,
ARC Epidemiology Unit/Professor of Rheumatology & Musculoskeletal Epidemiology
University of Manchester;
Anthony Timms, Laboratory Immunology Manager, Churchill Hospital Oxford;
Professor Adam Young, Consultant Rheumatologist, West Hertfordshire Hospital NHS
Trust/University of West Hertfordshire.

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Tom McBride, Will Palmer, Alex Scharaschkin, Omer Saka, Karen Taylor, Colin Ross, Philippa Dixon

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ERAN: Early Rheumatoid Arthritis Network
ERAS: Early Rheumatoid Arthritis Study
NOAR: Norfolk Arthritis Register
GPRD: GP Research Database

Economic models of identification and treatment of early rheumatoid arthritis

1 We developed two economic models to evaluate the potential financial impacts on the NHS, the wider economy in particular employment and the quality of life for patients of more early diagnosis and treatment of people with rheumatoid arthritis (RA). Both models are based on the NAO incidence estimate of 26,000 annually for England (see our Methodology).

2 The first model establishes the number of people with rheumatoid arthritis diagnosed within three months of symptom onset under current practice, and the associated costs of this. The model then compares current practice against two possible scenarios: both are reconfigurations of current practice towards a more proactive, integrated identification and diagnostic service between GPs and specialists. The aim of reconfigurations would be to promote rapid identification, referral and diagnosis of early cases of rheumatoid arthritis. The model considers the impact of such reconfigurations in terms of (i) the number of people diagnosed within three months and (ii) the associated costs.

3 The second model compares:

(i) the current practice in treatment of people with early rheumatoid arthritis, and its costs;

(ii) more rapid treatment of people with early rheumatoid arthritis, and the impact this would have on NHS costs, productivity and quality of life for people with rheumatoid arthritis.

4 The two models have been constructed separately to evaluate (i) the diagnosis pathway of rheumatoid arthritis and (ii) treatment patterns, in particular, the time treatment starts after symptom onset. There is, however, some overlap between the two models. For example, the second model also incorporates the period between onset of symptoms and diagnosis, the cost incurred through specialist consultations and GP consultations are included in both models for this period. Therefore, the results from the two models relating to cost should not be aggregated. The first model does not include treatment and monitoring costs after diagnosis, therefore, the cost savings or increases identified need to be looked at in the context of early treatment for people who are diagnosed early.

5 Probability and cost values for the models were obtained from NAO surveys, ERAN[a], NOAR[b], GPRD[c], NICE guidelines (2009), literature reviews and expert opinion. This paper sets out the two models, the assumptions made in their construction, the main findings generated and their limitations and caveats.

a Early Rheumatoid Arthritis Network: The Early Rheumatoid Arthritis Network (ERAN) has over 1000 early RA patients on their database recruited since 2002, collected from a group of centres in the UK and Eire (1 centre).

b Norfolk Arthritis Register: NOAR commenced recruitment in 1989 of new onset cases of inflammatory polyarthritis and has recruited over 3,500 incident cases.

c General Practitioner Research Database: the GPRD is the world's largest computerised database of anonymised longitudinal medical records from primary care that is linked with other healthcare data. Currently data are being collected on over 3.6 million active patients (approx. 13 million total) from around 488 primary care practices throughout the UK. It is the largest and most comprehensive source of data of its kind and is used worldwide for research by the pharmaceutical industry, clinical research organisations, regulators, government departments and leading academic institutions.

Model one: Earlier identification of rheumatoid arthritis

6 The model is a decision analytical model constructed using the software package TreeAge 2008 Professional. **Figure 1** shows the model structure.

7 The model reconstructs a snapshot of the patient pathway up to diagnosis. It looks at the identification and diagnosis process of people with early rheumatoid arthritis, from onset of symptoms; presentation to GP (or other NHS services such as Accident and Emergency); GP referral to specialists; and, ultimately, diagnosis. It compares the costs to the NHS which are incurred at each stage of this identification process. This includes costs of: GP consultations; consultations with a rheumatoid arthritis specialist and the diagnostic tests undertaken (see **Figure 2 on page 6**).

8 A variety of approaches exist, which encapsulate a more proactive, integrated service between GPs and specialists, along the lines of Early Arthritis Clinics. What these approaches have in common is a close integration between GPs and specialists and a communication mechanism in place which promotes understanding and application of clear rapid referral criteria for GPs in respect of suspected cases of rheumatoid arthritis. We have characterised these approaches collectively as an Early Arthritis Clinic (EAC) approach.

9 The population covered by the model includes all people who may have undifferentiated arthritis (UA)[d] (defined as people with symptoms similar to inflammatory arthritis which also include non-inflammatory arthritis such as osteoarthritis). Increased GP awareness and understanding of inflammatory arthritis (including rheumatoid arthritis)[e] could lead to increased early diagnosis, but it could also lead to increased visits to consultants of people with non-inflammatory UA. It could also, however, reduce the number of repeated visits made by people to their GPs and avoid the potential duplication of diagnostic tests requested by GPs which are then also requested by specialists after referral. The model accounts for the effects of an Early Arthritis Clinic approach upon people with suspected rheumatoid arthritis as well as the unintended effects on people with non-inflammatory arthritis with similar symptoms presenting. It also captures the corresponding impact on NHS resource utilisation for all UA patients under both scenarios.

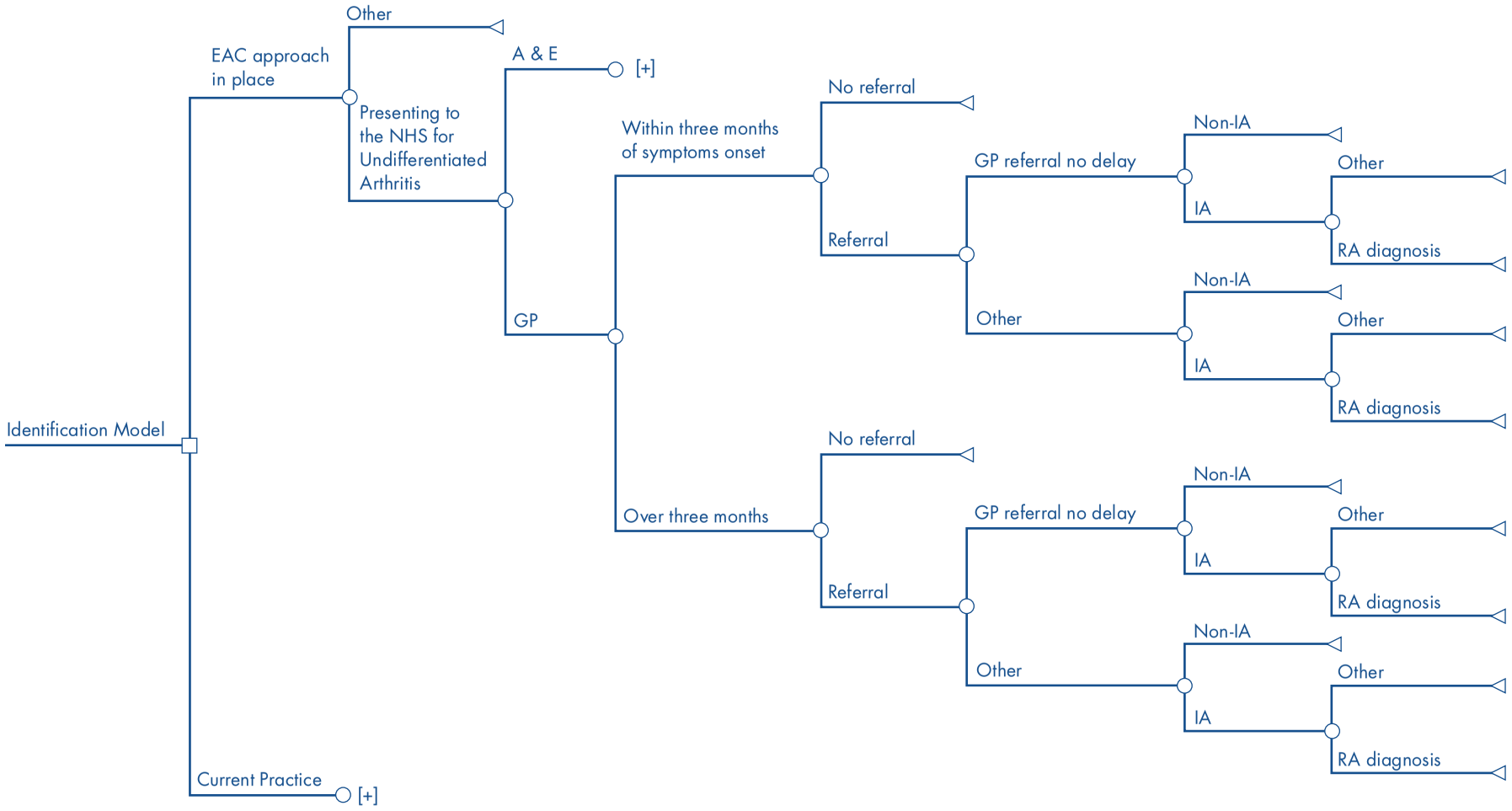
10 The model combines incidence rate estimates, probability of transition from one stage to the next and resource utilisation at each stage. For each scenario, the total cost of the diagnostic process is derived by combining volumes with the unit cost of service provision at each stage in the process (paragraph 7).

11 We also explored the impact of a campaign to increase public awareness of inflammatory arthritis, including rheumatoid arthritis, with the aim of increasing the proportion of people with rheumatoid arthritis who present early to their GP.

d UA (Undifferentiated arthritis): defined as that illness with symptoms similar to inflammatory arthritis which are difficult to differentiate from one another, and are likely to be referred under the referral criteria recommended by a typical EAC approach. This typically includes about 50 per cent non inflammatory arthritis patients such as those with osteoarthritis.

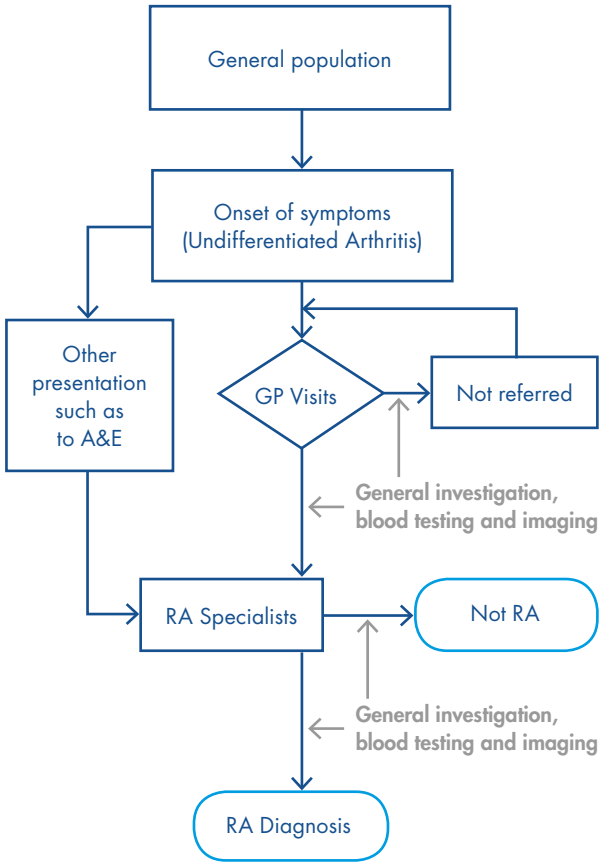
e IA: inflammatory arthritis. It includes conditions such as rheumatoid arthritis, ankylosing spondylitis, lupus and Reiter's syndrome, with rheumatoid arthritis as one of the most severe forms.

1 Decision tree model to compare the cost and the number of patients diagnosed within three months with current service provision against a rapid referral system (EAC approach) for patients with recent onset of symptoms of rheumatoid arthritis (RA)



Source: National Audit Office

2 Patient pathway to diagnosis and service utilisation at each stage



Source: National Audit Office

Probabilities

12 **Figure 3** sets out the probabilities used in the model and their sources. The Figure also shows the range of probabilities that were examined in sensitivity analyses that were run in the model (these are discussed further below).

13 Probabilities on current practice have been estimated using data from the GP Research Database; consultant collected data from the Early Rheumatoid Arthritis Network; mainly GP collected data from The Norfolk Arthritis Register; the NAO survey of people with rheumatoid arthritis; and published literature on early diagnosis of rheumatoid arthritis.

14 Probabilities with a rapid referral service in place have been estimated from studies of EAC (Early Arthritis Clinics)[1], for which the validity of EAC criteria was reported by van der Helm van Mil A et al. (2008)[2].

3 Probabilities used in the model

Parameter	Baseline Value	Range	Source
Incidence and presentation of people with rheumatoid arthritis			
Overall incidence of rheumatoid arthritis in the working age population	0.00062	(0.00035-0.00062)	Wiles N et al. (1999)[1] Weighted with gender and age distribution in England; NAO analysis of GPRD data between 2003-07
Probability of presenting to GP within three months	0.4	0.25-0.50	NAO patient survey (0.5), NOAR (0.25), Kumar K et al. (2007)[2] (0.5)
Probability of person presenting with symptoms of Undifferentiated Arthritis (UA)	0.00186		Derived from: Gormley GJ et al. (2003)[3] and NAO incidence estimate of RA
Probability of person having Inflammatory Arthritis (IA) (which could be rheumatoid arthritis or other IA)	0.5	(0.4-0.6)	van dB et al. (1998)[4] Gormley GJ et al. (2003) Van Aken J et al. (2005)[5]
Probability of having rheumatoid arthritis amongst people who present with IA	0.7		van dB et al. (1998) Machold KP et al. (2002)[6]
GP activity			
For those presenting within three months, the probability of being referred within three months of onset	0.6	(0.5-0.8)	Estimate: 80 per cent inferred from NAO Patient survey, Kumar et al. (2007) reported 60 per cent, NAO analysis of ERAN data (40 per cent referred within three months of symptoms onset)
Average number of GP visits for patients before referral for those not referred on first visit	4	(2-6)	The Kings Fund (2009)[7]
Probability of GP referral on first visit	0.21	(0.10-0.25)	The Kings Fund (2009)
Probability of GP referral for non-IA patients with UA	0.50	(0-1)	From analysis of 18 weeks data, rheumatology patients constitute less than 20 per cent of all new cases referred to rheumatology units. From our personal communication with A Miller at Nuffield Orthopaedic Centre, Oxford on its recent audit on Rheumatoid Factor (RF) testing, out of 62 cases referred to rheumatology units for diagnosis, only 34 patients were confirmed with IA (5 cases with missing data). We assumed that 50 per cent of UA patients following presentation to GP were currently referred to RA specialists for diagnosis.
Specialist activity			
Probability of diagnosis on referral (within three months of onset of symptoms)	0.4	(0.33-0.51)	The NAO patient survey found that 69 per cent of people with rheumatoid arthritis were seen within 18 weeks of referral and 74 per cent were diagnosed within three months of being seen. Therefore the maximum probability of these patients being diagnosed within three months is 0.51 (0.69 x 0.74). Analysis of ERAN data shows that 33 per cent of patients not on treatment before seeing a consultant were being treated within three months of onset, so the minimum probability of being diagnosed within three months of symptom onset is 0.33.

3 Probabilities used in the model *continued*

Parameter	Baseline Value	Range	Source
Diagnostic tests – Probability of tests being carried out by GPs before referral to a specialist on a person with suspected rheumatoid arthritis			
Probability of a GP carrying out a rheumatoid factor (RF) test	0.49	(0.46-0.52)	NAO patient survey (0.49) GPRD (0.52)
Probability of a GP carrying out a C-reactive protein (CRP) test	0.56		GPRD
Probability of a GP carrying out an erythrocyte sedimentation rate (ESR) test	0.60		GPRD
Probability of a GP carrying out an anti-cyclic citrullinated peptide antibody (anti-CCP) test	0.12		NAO patient survey
Probability of a GP carrying out a Full Blood Count (FBC) test	0.75		GPRD
Probability of a GP carrying out an x-ray	0.09	(0.09-0.22)	NAO Survey (0.09) and GPRD 2007 analysis (0.22)
Probability of a GP carrying out the above test on non-IA undifferentiated arthritis patients	0.5	(0-1)	Personal communication with A Miller at Nuffield Orthopaedic centre Oxford indicated that RF tests were requested for a wider range of patients other than RA patients such as osteoarthritis. According to their audit less than 50 per cent of RF tests were for patients with RA. We assumed that similarly those other tests were also requested by GPs for other non-IA UA patients. In the base case analysis, we assumed the probability for referral for non-IA UA was 50 per cent.
Diagnostic tests - Probability of tests being carried out by consultants on a person with suspected rheumatoid arthritis			
Probability of a consultant carrying out a RF test	0.6		NAO patient survey
Probability of a consultant carrying out an anti-CCP test	0.68		NAO patient survey
Probability of a consultant carrying out an x-ray	0.69		NAO patient survey
Early Arthritis Clinic: probabilities			
Probability of diagnosis within three months once referred in an Early Arthritis Clinic approach	0.51	(0.4-0.75)	Van de Helm van Mil et al. (2008)[8] reported about 75 per cent RA patients could be predicted following the criteria used in EAC. Raza K et al. (2005)[9] reported anti-CCP and RF test have a sensitivity of over 48 per cent. Discussion with those deploying an EAC approach suggests that almost all patients could be seen within 4 weeks of referral, with an average of less than two weeks. Van dB et al. (1998) reported that 70 per cent of RA patients were diagnosed within two weeks of referral. Based on these and some other literature reviews, a conservative 0.51 is assumed for the base case analysis, and a range of 0.4 to 0.75 is assumed for sensitivity analysis.

3 Probabilities used in the model *continued*

Parameter	Baseline Value	Range	Source
Probability of tests being carried out by an Early Arthritis Clinic (Anti-CCP, CRP, 0.69*x-ray, RF-test)	1		Anti-CCP, CRP, and RF-test were assumed for all IA patients as suggested by Van D Helm van Mil A et al (2008), although in practice, those tests won't be requested by specialists for all patients. This would lead to an overestimate of the tests cost under an EAC approach. X-ray was assumed to have the same probability of being requested by consultants as currently. It is assumed that a GP would refer all patients with symptoms of UA on presentation to an Early Arthritis Clinic, following an EAC protocol for UA.
Probability of consultants carrying out the above tests on non-IA UA patients	0.5		Our discussion with A Miller on her recent audit work on Rheumatoid Factor tests indicates that consultants are much less likely to request tests inappropriately than GPs, to be conservative, a probability of 0.5 (the same as GP) was assumed here.

NOTES

1 Wiles N et al. (2002) Estimating the incidence of rheumatoid arthritis. Arthritis & rheumatism. 42, No. 7, July 1999, pp 1339–1346.

2 Kumar K et al. (2007) Delays in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. Rheumatology 2007; 46: 1438-1440.

3 Gormley G. J. et al. (2003). Can diagnostic triage by general practitioners or rheumatology nurses improve the positive predictive value of referrals to early arthritis clinics? Rheumatology 2003; 42 (6):763-768.

4 van dB et al. (1998) Diagnosis and course of early-onset arthritis: Results of a special early arthritis clinic compared to routine patient care. British Journal of Rheumatology Vol 37, 1084-1088.

5 Van A J et al (2006) Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis 2006; 65:20-25.

6 Machold KP et al. (2002) Very recent onset arthritis--clinical, laboratory, and radiological findings during the first year of disease. J Rheumatol. 2002 Nov;29(11):2278-87.

7 The Kings Fund (2009) Perceptions of patients and professionals on rheumatoid arthritis care (January 2009). www.rheumatoid.org.uk/article.php?article_id=617.

8 Van de Helm van Mil et al. (2008) Validation of a Prediction Rule for Disease outcome in Patients with Recent onset Undifferentiated Arthritis. Arthritis & Rheumatism Vol 58, No. 8, August 2008, pp 2241–2247.

9 Raza K et al. (2005) Predictive value of Antibodies to Cyclic Citrullinated Peptide in Patients with Very Early Inflammatory Arthritis. The Journal of Rheumatology 2005; 32: 231-8.

10 All GPRD data relate to 2007.

Costs

15 **Figure 4** details the costs used in the model and their sources. The following costs to the NHS are included in the model: GP consultations; consultations by consultants; laboratory tests, both those carried out by GPs prior to referral and those carried out by specialists after referral (x-ray, anti-CCP, CRP, RF test). This model only focuses on the diagnosis pathway and no treatment and monitoring costs after diagnosis are included.

Assumptions

16 Overall, the assumptions made in the model are conservative, to minimise the risk of overstating the effects of the parameters within the model.

17 The main assumptions in our first model are:

i **The population who go to see their GP with symptoms of (Undifferentiated Arthritis) is three times the incidence of rheumatoid arthritis.** The incidence of people with undifferentiated arthritis (UA) is made up of people with inflammatory arthritis (such as rheumatoid arthritis) and non inflammatory arthritis (such as osteoarthritis). Studies suggest that UA has three times the incidence of rheumatoid arthritis.[3] We have used this rate irrespective of whether people go to an EAC or not.

ii **Of those people with suspected rheumatoid arthritis who present within three months of symptom onset and are referred to a specialist within three months of symptom onset, sixty per cent are referred upon their first visit to their GP.** This is much more conservative than suggested by The Kings Fund, whose survey found that just 21 per cent of patients were referred after a first visit to their GP.[4]

iii **People with non-IA who are referred by GPs in current practice visit their GP only once, the probability that a test will be requested by GPs for those patients will be 50 per cent of that for IA patients, and the probability of referral for those patients is 50 per cent.**

iv **Of those people referred within three months, 40 per cent are diagnosed by a specialist within this period.** From our analysis of ERAN data, the NAO patient survey, and literature review, between 33 and 45 per cent of those referred within three months of onset are currently diagnosed by a specialist within this period.

v **People who present to Accident and Emergency rather than to a GP have one consultation before they are referred to a specialist.** When people present to A&E, we have also assumed that the same proportion present within three months of disease onset as present to GPs.

vi **For current practice, where we have no data of the probability of a specialist requesting a test to be carried out after referral, to be conservative, we have assumed that the tests requested by a GP are not repeated by the specialist.** For some tests, such as ESR, there is a probability of 0.6 that a GP will request the test to be carried out, but we have no data on requests by specialists in the current setting, so we assumed that there was no ESR test requested by consultants.

vii **An EAC can be specialist nurse led, registrar or consultant led. We assumed that such a service is led by a rheumatology consultant. In an EAC approach, the probability of someone with suspected rheumatoid arthritis being diagnosed within three months of referral is 0.51.** This probability is conservative as it lies in the upper range of the estimates for current practice (Figure 3). Evidence suggests, however, that in an EAC approach, all suspected cases of rheumatoid arthritis are seen by specialists within two to four weeks of referral.[5]

viii **All people with IA referred under an EAC approach are tested with anti-CCP, RF, CRP with x-ray assumed to be requested at the same level as currently requested by specialists. The probability of testing on non-IA patients is assumed to be 50 per cent of those for IA patients.** There is no duplication of these tests for patients referred under a rapid referral system from GPs to specialists; that is, the tests take place only once for the purpose of diagnosis. Although our personal communication with A Miller at Nuffield Orthopaedic Centre, Oxford indicates that specialists are much less likely to request a test inappropriately, we assumed the same level of testing on non-IA patients as carried out by GPs.

ix **The cost of tests for ultrasound and MRI scans are not included.** These tests are usually carried out at the request of specialists and it is therefore unlikely that service reconfiguration would result in a change to when these tests are carried out in the pathway (and therefore costs would still fall to the specialist part of the process).

4 Cost parameters used in the identification model

Parameter	Cost (£)	Source
Cost of consultations		
Consultant consultation for rheumatoid arthritis patients (initial)	161 (94-215)	NHS schedule of reference costs (2007-2008): 410[1], which is £156. This is then adjusted with CPI for medical services (index base 2005 as 100, 2007: 105; 2008: 109[2], 161=156*(109/105)
GP consultation for RA patients	60 (36-61)	The average cost for consultant consultation from Unit Cost of Health and Social care[3] is £93 and the average cost from NHS reference price for consultant consultation with RA patients is £156, this suggests that RA patients need a longer consultation time. We assumed that similarly the cost for GP consultation with RA patients was higher than the average for all patients due to the nature of the disease. PSSRU reported that on average GP consultation time is 11.7 minutes, by applying the ratio of 156/93, we assumed that the average consultation time for an RA patient by a GP is 20 minutes (20= (156/93)*11.7), PSSRU estimated on average it costs £3 per minute for GP consultation, so the cost per consultation for RA patients is estimated to be £60.
A & E visit	87	Curtis L (2009) Unit cost of Health and Social Care (2007-2008)
Cost of diagnostic tests		
Full Blood Count (FBC)	7.12	These prices were constructed from adding together: (i) Test prices (ii) Cost of blood sample collection (iii) Cost of blood sample transportation. Test prices are based on quotations from Churchill Hospital Oxford which provide tests for Nuffield Orthopaedic Centre and adjusted using NHS reference Market Force Factor for Nuffield Orthopaedic Centre NHS trust which is 103[4]. A blood sample is either taken at GP practice (most of the cases) then sent to test centre or a sample might be taken at the test centre. The cost for collecting blood sample by phlebotomists is estimated to be £3 per sample (including direct cost and indirect cost). This is based on a typical salary of £18,500 per annum for a phlebotomist, who works 37.5 hours per week and 41.7 working weeks (PSSRU) plus capital and other indirect overheads per head as estimated by PSSRU (2008) It is assumed on average a phlebotomist takes 10 blood samples per hour. A transportation charge of £1 per sample is assumed. The £4 estimate for sampling and transporting blood sample is in line with the £3-4 surcharge for blood samples taken at a test centre.
Rheumatoid Factor test (RF)	11.25	
Erythrocyte sedimentation rate test (ESR)	5.56	
C-reactive protein test (CRP)	5.54	
anti-cyclic citrullinated peptide antibody test (anti-CCP)	18.51	
X-ray	134	Taylor et al. (2008)[5]

NOTES

1 Department of Health (2009) NHS schedule of Reference cost (2007-2008): 410. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.

2 Office for National Statistics (ONS) Consumer Price Indices. www.statistics.gov.uk/statbase/TSDdownload1.asp.

3 Curtis L (2009) Unit Cost of Health and Social Care (2007-2008) (PSSRU). www.pssru.ac.uk/uc/uc2008contents.htm.

4 Department of Health (2009) NHS schedule of Reference cost (2007-2008). www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.

5 Taylor M et al. (2008) The relationship between HAQ score and resource use in the management of Rheumatoid Arthritis Poster Presentation. European League against Rheumatism Annual Conference. Paris, France, June 2008.

Baseline results

18 Based on the adult (over 16) population (2007) for England and the NAO incidence estimate of 26,000 for rheumatoid arthritis, there are currently around 72,000 patients with UA presenting to the NHS annually with or without an EAC. Of these, 54,500 would be referred in the current steady state of service provision. With an EAC approach, all 72,000 patients would be referred. **Figure 5** illustrates the number of patients going through the model with or without an EAC approach in place.

19 Currently, about 25-50 per cent of patients present themselves to a GP within three months of symptom onset, and about 50-80 per cent of those are then referred to a specialist within this period. Assuming 40 per cent of those with the condition present within three months of symptom onset and 60 per cent of those are then referred to a specialist within the same period, our model for identification suggests that annually about 2,600 people with rheumatoid arthritis in England are diagnosed within three months of symptom onset. (**Figure 6**, first column).

20 We examined two scenarios incorporating a rapid referral and diagnosis system (EAC approach), whereby GPs follow a well defined algorithm for referring UA patients as suggested by research on Early Arthritis Clinics[6]. If 80 per cent of people with suspected rheumatoid arthritis presented within three months, and were referred within an EAC framework, assuming half were diagnosed immediately after referral (within two weeks), then 4,300 could be diagnosed within three months with a saving of £1.8 million (Figure 6, scenario 1); if 75 per cent were diagnosed as suggested by Van der Helm van Mil A et al. (2008), then 6,300 would be diagnosed (Figure 6, scenario 2).

Sensitivity analysis

21 The inputs to the model are subject to various degrees of uncertainty. We carried out sensitivity analyses on various parameters to test the impact of the uncertainty upon the incremental costs. **Figure 7** shows the effect of varying the parameters used in the model upon the *incremental costs*. It indicates that the most significant drivers of incremental costs in the model are:

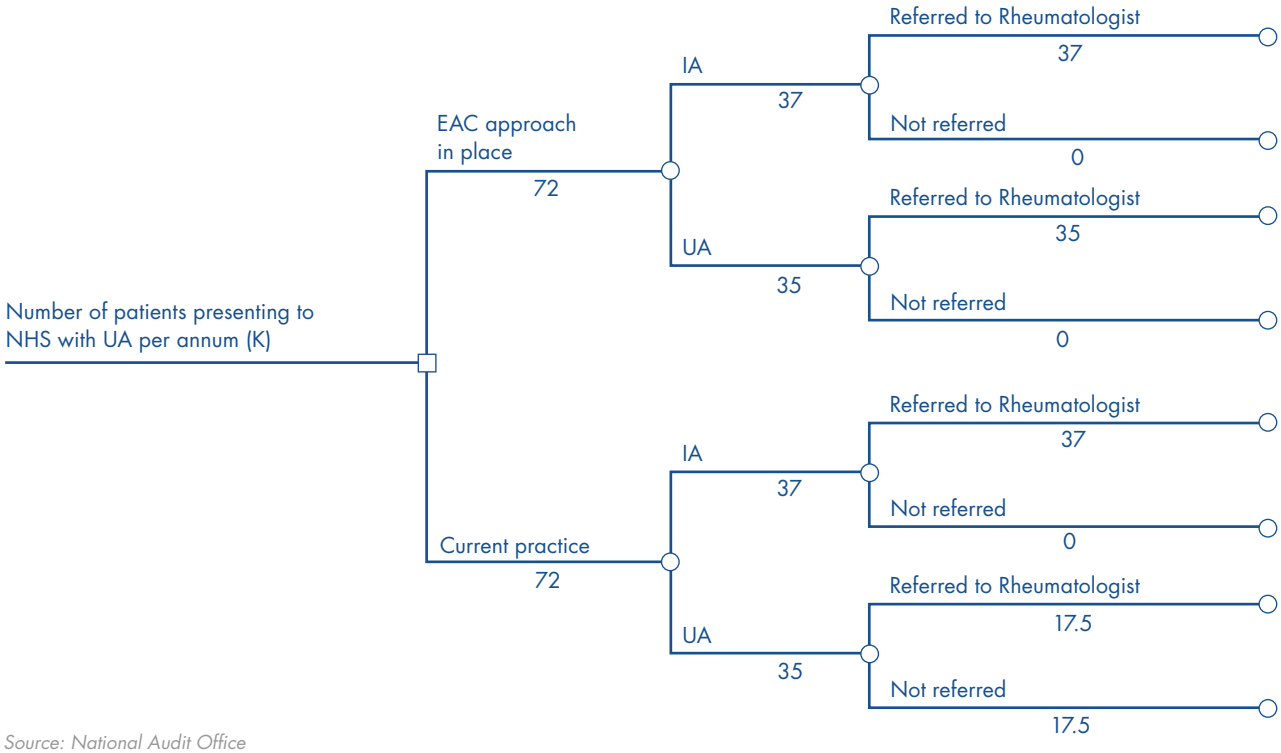
(i) Probability of inappropriate referral for non-IA UA patients in current practice;

(ii) The number of GP visits before diagnosis;

(iii) Probability of having IA for patients presenting with UA: 0.4 to 0.6;

(iv) Probability of GP carrying out tests on non-IA UA patients.

5 Patients flow in the baseline model



Source: National Audit Office

6 Potential cost savings to diagnostic services from an EAC style rapid referral system to increase the number of people diagnosed with rheumatoid arthritis within three months of symptom onset

	Current Practice	Scenario 1	Scenario 2
Annual incidence of people with rheumatoid arthritis	26,000	26,000	26,000
Percentage of people with rheumatoid arthritis presenting within three months[1]	40	40	40
Percentage of people with rheumatoid arthritis referred to a specialist within three months	60	80	80
Percentage of people being diagnosed by a consultant within three months once referred	40	51	75
Total number of people diagnosed with rheumatoid arthritis within three months	2,600	4,300	6,300
Percentage of total annual incidence (26,000)	10	17	24
Cost savings generated through an EAC approach (£ million)		1.8	1.8
Attributable to diagnostic test		0.2	0.2
Attributable to consultant consultation		(2.7)	(2.7)
Attributable to GP and A&E consultation		4.3	4.3

Source: National Audit Office

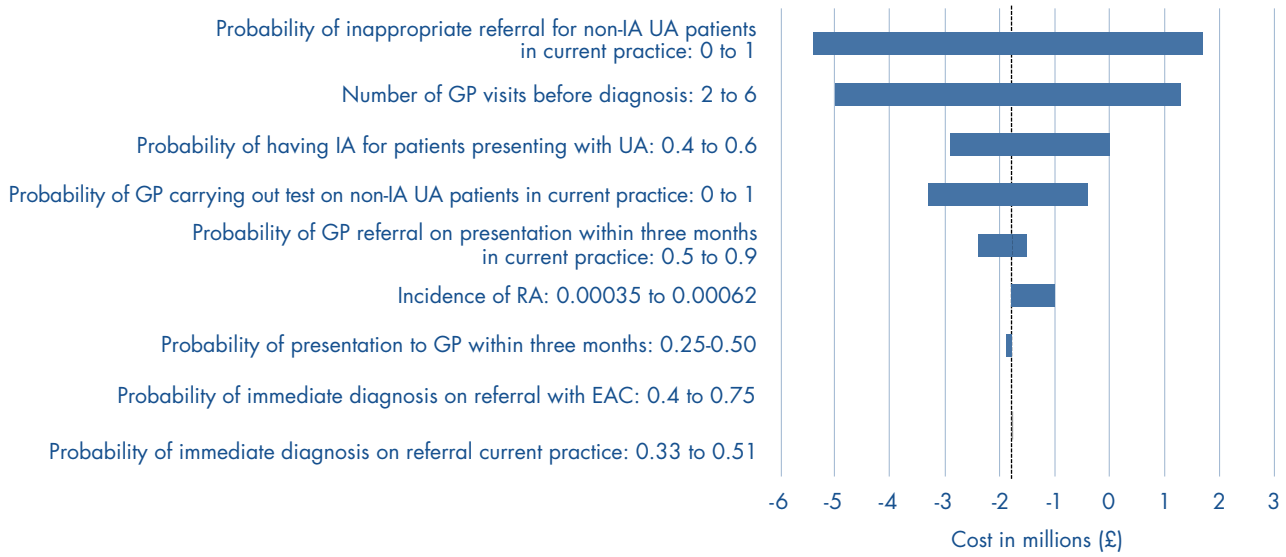
NOTES

1 In the base-case analysis, the proportion of people presenting to a GP within three months is held constant at 40 per cent. We also examined the impact of increasing the proportion of people with rheumatoid arthritis presenting within three months, for example through use of a public awareness raising campaign in respect of rheumatoid arthritis. This is reported in the sensitivity analysis.

2 Cost to GP, consultant and diagnostic tests may not add up to the total cost savings due to the rounding of the figures.

7 The main determinants of incremental costs in the identification of early rheumatoid arthritis

Tornado diagram showing current practice composed to an EAC approach



Source: National Audit Office

22 We also carried out sensitivity analyses to test the impact of the uncertainty upon the *incremental effectiveness*, that is, the increased number of people with rheumatoid arthritis identified within three months. **Figure 8** shows the effect of varying the parameters used in the model upon the number of people diagnosed within three months. It indicates that the most significant drivers of incremental effectiveness in the model are:

(i) The probability of immediate diagnosis on referral with an EAC approach;

(ii) The probability, after presentation, of GP referral within three months of symptom onset;

(iii) The incidence rate of rheumatoid arthritis.

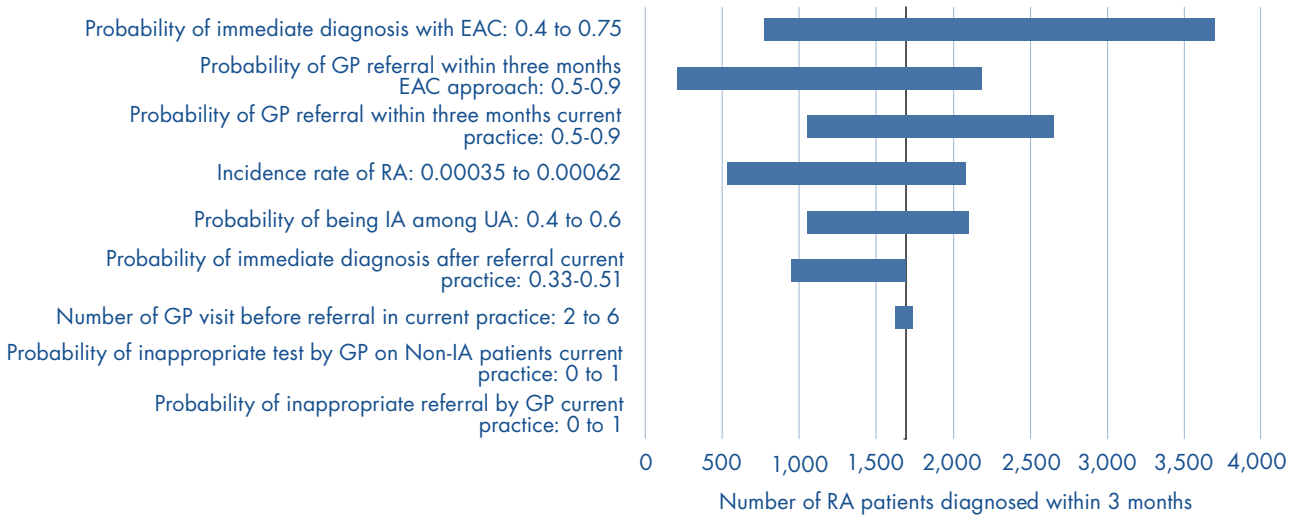
23 We performed deterministic sensitivity analyses to test the effect on the model results of the drivers of incremental costs and incremental effectiveness identified above, as well as the effects if there were a public awareness campaign to increase the percentage of patients presenting early (within three months). **Figure 9** summarises the results from these analyses.

24 The probability of a person having Inflammatory Arthritis amongst people with Undifferentiated Arthritis has a major impact on incremental cost. This reflects that the appropriateness of GP referral and the extent to which GPs request tests to be carried out on non-IA patients in current practice affect service utilisation. In the base-case analysis, we assumed a probability of 50 per cent for inappropriate testing and inappropriate referral for non-IA UA patients. However, If inappropriate tests are currently requested on 100 per cent of non-IA UA patients, the cost saving could be £3.3 million *(sensitivity analysis 5)* and if there is an 80 per cent chance that those patients are referred to a specialist as well, the cost saving could be as high as £6.2 million *(sensitivity analysis 6)*.

25 The incremental cost is very sensitive to the number of GP visits. If the cost of a GP consultation is £36 instead of being £60, under the base case scenario, it could be cost neutral (*sensitivity analysis 1*). However, if we apply an average of four visits to a GP before referral for all patients[7], then the cost saving could be £3.3 million *(sensitivity analysis 2)*. If we apply an average of three visits to a GP before referral, then the cost saving could be £1.2 million *(sensitivity analysis 3)*. We also explored the impact of the number of GP visits for non-IA UA patients before referral. If we assume that patients with non-IA UA visit a GP twice before being referred, then the cost saving could be much as £8 million (*sensitivity analysis 4*).

8 The main determinants of incremental effectiveness (number of people identified within three months) in the identification of early rheumatoid arthritis

Tornado diagram showing current practice compared to an EAC approach



Source: National Audit Office

9 Sensitivity analysis examining cost and effectiveness of service reconfigurations

Diagnosis	Patients presenting within three months %	Patients referred within three months %	Patients diagnosed within three months once referred %	Total number of patients diagnosed within three months	Cost Savings (£m)
Base case (result from model Scenario one)	40	80	51	4,300	1.8
Sensitivity analysis 1 (GP cost £36 per visit)	40	80	51	4,300	(0.1)
Sensitivity analysis 2 (current practice, all IA patients visit GPs on average 4 times)	40	80	51	4,300	3.3
Sensitivity analysis 3 (current practice, all IA patients visit GPs on average 3 times)	40	80	51	4,300	1.2
Sensitivity analysis 4 (Current practice: 4 GP visit, for non-IA UA patients)	40	80	51	4,300	8.0
Sensitivity analysis 5 (Current practice inappropriate test probability 1)	40	80	51	4,300	3.3
Sensitivity analysis 6 (Current practice inappropriate test probability 1 and inappropriate referral probability 0.8)	40	80	51	4,300	6.2
Sensitivity analysis 7 (increase in probability of early diagnosis to 0.65)	40	80	65	5,400	1.8
Sensitivity analysis 8 (increase in probability of early diagnosis to 0.8)	40	80	80	6,700	1.8
Sensitivity analysis 9 (increase in probability of early referral to 0.9; and early diagnosis to 0.8)	40	90	80	7,500	1.8
Sensitivity analysis 10 (increase in probability of presentation to GP within three months to 80 per cent; with no increase in non-IA patients)	80	80	51	5,900	1.8
Sensitivity analysis 11 (increase in probability of presentation to GP within three months to 80 per cent; with no increase in non-IA patients)	80	80	75	13,000	1.8
Sensitivity analysis 12 (increase in probability of presentation to GP within three months to 80 per cent; with 100 per cent increase in overall presentation due to UA)	80	80	51	5,900	(3.7)
Sensitivity analysis 13 (increase in probability of presentation to GP within three months to 80 per cent; with 200 per cent increase in overall presentation due to UA)	80	80	51	5,900	(9)
Sensitivity analysis 14 (increase in probability of presentation to GP within three months to 80 per cent; with 200 per cent increase in overall presentation due to UA and 25 per cent of those presenting due to the awareness campaign being referred to a specialist but subsequently found not to have UA)	80	80	51	5,900	(13)

Source: National Audit Office

NOTE

Sensitivity Analyses (10-14) assume a public awareness campaign is run, with the effect of increasing the percentage of people with RA presenting in three months, as well as increasing the number of people with UA who present to a GP. The cost of such a campaign is not, however, included in the analyses.

26 Irrespective of the incidence of rheumatoid arthritis, the number of people with rheumatoid arthritis diagnosed within three months could be affected by transition probabilities at each stage in the pathway (see paragraph 12). However, service configuration is mostly influenced by the speed with which people with rheumatoid arthritis are diagnosed on referral and the proportion of patients being referred by GPs within three months. As *sensitivity analysis 9* shows, the number of patients diagnosed early could rise to as much as 7,500 with a scenario where GPs refer 90 per cent and specialists diagnose 80 per cent respectively within three months.

27 We also explored the impact of a campaign to raise public awareness of rheumatoid arthritis among the general public on the number of people diagnosed within three months and the impact on costs to the NHS (see sensitivity analyses 10-14). We did not take account of the cost of any such awareness campaign. We assumed the impact of the campaign could double the percentage of patients presenting early to 80 per cent; if 75 per cent could be diagnosed promptly with an EAC approach with no extra non-IA patients seeking GP consultation, this could increase the people diagnosed within three months to as much as 13,000 (*sensitivity analysis 11*) with no increase in cost. However, it is likely that there would be extra patients seeking GP advice following such a public campaign. In a scenario with a 100 per cent increase in patients presenting to GP, this would lead to an incremental cost of £3.7 million (*sensitivity analysis 12*); if there were an increase of 200 per cent (three times as many as before the campaign), then this could rise to £9 million (*sensitivity analysis 13*). And if some of those presenting to a GP were subsequently referred inappropriately, say with a 25 per cent probability, the incremental cost could rise by up to £13 million (*sensitivity analysis 14*).

Conclusion and discussion

28 A reconfiguration of the identification and diagnostic service between GPs and specialists, whereby an EAC approach for people with recent onset of rheumatoid arthritis symptoms is applied, could reduce annual NHS costs as well as increasing the number of people with rheumatoid arthritis diagnosed within three months of symptom onset. The cost saving would be realised through a reduced number of repeat visits to a GP by people with suspected rheumatoid arthritis, and a reduced number of requests by GPs for diagnostic tests before referral.

29 The parameters used in the model were from various sources. These values have been triangulated against each other and conservative values have been chosen with regard to the cost and resource utilisation in current practice, and the incremental effectiveness which could arise from a reconfigured service.

30 The sensitivity analyses have demonstrated the robustness of our conclusion that an EAC approach is cost effective. The main drivers of resource utilisation are (i) the referral behaviour of GPs and (ii) the activities of GPs prior to referral, in particular in terms of diagnostic testing. The effects on early diagnosis arise at all stages of the pathway. An EAC approach could help to identify more people with recent onset rheumatoid arthritis within three months. Furthermore, our communication with acute trusts with an EAC approach indicates that specialist nurses or registrars conduct the majority of consultation, whereas in our analyses we assumed that all consultations were conducted by consultants. Our model is therefore likely to underestimate the potential efficiency gains.

31 The model assumes that there is sufficient specialist capacity to cope with the increased volume of referrals. Our survey and analysis of NOAR data indicate that currently around 80 per cent of patients will be referred within the first year of symptom onset, therefore, following an EAC approach, if all patients currently referred already are referred within the first year, plus the 17,500 (see Figure 5) extra referrals as suggested from the model, there would be a maximum of one-off surge of around 32,000 extra referrals initially (17,500+57,400*0.2), equivalent to around 200 per acute trust. Once a steady state is reached again under an EAC approach, the extra referrals would be likely to be under 17,500 per annum, about 110 per trust each year. Our census of acute trusts shows that currently one third of trusts already have an EAC approach, so the net increase in referrals would be about one third lower than this estimate.

32 Based on this estimate of patient flow, the cost to secondary care due to the initial spike in referrals could be in the region of £3.6m. The adoption of this approach could however, result in an initial cost saving to primary care of about £3 million (assuming the average cost for a GP consultation is £36, if a cost of £60 is assumed, the cost savings could be around £5 million) through reduced GP visits for patients with new onset of symptoms and the avoidance of unnecessary diagnostic testing requested. As in the base case analysis, once a steady state is reached, this approach could generate annual efficiency savings for the NHS of about £2 million mainly through reduced service utilisation in primary care.

33 The model did not account for the initial investment that might be needed for an EAC approach to be more widely established. Our analysis of spending on rheumatoid arthritis patients by acute trusts with and without an EAC as reported to the NAO, showed no significant difference in spending. An EAC can either be consultant or specialist nurse led. For those trusts which have an EAC approach in place, the key features are: a specialist nurse (band 7) trained in joint assessment; rapid access to musculoskeletal ultrasound radiologist service (or rheumatologist or specialist nurse trained to use such machines); and sufficient administrative support to direct patients rapidly into the EAC and ensure patients receive correct information on time. For rapid referral to be in place, GPs also need to be aware of the referral criteria so that they can refer patients promptly when patients present to them. The investment is more in terms of time needed to train the staff (for example, it normally takes up to two years to train a specialist nurse) and have a management system in place, rather than in physical expenditure on purchasing equipment. A musculoskeletal ultrasound machine may be the major physical purchase if a unit does not already have access to one.

34 However, the model evaluated here did not take into account the contributions of ultrasound imaging to the effectiveness of diagnosis in an EAC approach, and an EAC is normally part of a rapid referral system for both early rheumatoid arthritis patients and established patients with a flare-up and in need of emergency care. Edwards (2009)[8] reported that patients cared for through a rapid referral system accounted for less than 30 per cent of the total patients, with the rest accounted for mostly by flare-ups in need of urgent care. In addition, other inflammatory arthritis conditions other than rheumatoid arthritis, such as ankylosing spondylitis, which also need early treatment, will inevitably benefit from such an approach, and these benefits are not captured here.

35 We explored the impact of a public awareness campaign (without considering the campaign cost itself) upon the likely increase in service utilisation and the corresponding cost to the NHS. This analysis is exploratory, as there is no available evidence on the impact of a public awareness campaign on those parameters assumed here. However, even in the most costly scenario assumed here (*sensitivity analysis 14*), the cost per case identified within three months is £2,100, and this cost could potentially be offset by the productivity gains through early treatment as demonstrated in Model 2. As such a campaign will invariably lead to early diagnosis of other inflammatory arthritis, which also benefits from early identification and treatment, the net benefits will be higher.

Limitations and Caveats

36 This is a decision analytical model which attempts to evaluate the cost effectiveness of alternative strategies of early diagnosis of rheumatoid arthritis in England. We have used data in such a way as to produce conservative outputs from the model. The model is intended to examine the opportunities for configuring the diagnostic service for rheumatoid arthritis along the lines of an EAC approach, by probing the impact of the main drivers in the rheumatoid arthritis diagnosis pathway.

37 To do this, we focussed on establishing baseline and incremental costs rather than total costs. We therefore concentrated on evaluating the impact of changes in configuration on increasing numbers of people diagnosed early, and the associated costs. In doing so some cost elements (such as the cost of MRI scans) have not been included as they do not have an impact on service utilisation patterns under differently configured diagnostic service scenarios. Some costs have also not been included where we lacked information. The figures in the model are indicative, whilst attempting to be as accurate and representative of the real setting as the data allow.

38 The parameters used in the model were from different sources, all of which are subject to their own biases and limitations. Some deterministic sensitivity analyses have enabled us to explore these limitations (for example examining the impact of varying the number of GP visits before referral).

39 Since the studies on Early Arthritis Clinics which informed the analyses and the benefits of an Early Arthritis Clinic approach were carried out some time ago, they will not fully reflect the latest developments in early diagnosis of rheumatoid arthritis. Therefore the model could underestimate the effectiveness of more widespread adoption of such an approach.

40 We implicitly assumed in the model that there is sufficient specialist capacity to cope with a sharp increase in referral of people with suspected rheumatoid arthritis, and the consequent increase in the number of people diagnosed early. In practice, however, the extent to which this is applicable in the short-term is constrained by the number and availability of rheumatology specialists.

41 In contrast to the cost estimated by NICE for implementing the NICE guidelines[9], which estimated an increase of £9 million in implementing the recommendations for early rheumatoid arthritis patients, we have demonstrated a cost saving to the NHS from a similar approach. This arises because NICE included other monitoring costs during the first year after diagnosis (assuming adoption of NICE 2009 guidelines), while we focused on the diagnosis pathway up to diagnosis only. Furthermore, while NICE focused on the short-term costs to the acute sector, we also included the offsetting impact of reduced costs to primary care (for example GPs requesting tests, and repeated visits to GPs prior to referral to specialists).

42 The cost savings demonstrated in the model may not be realised by the NHS in the short-term, as increases in the number of people diagnosed with early rheumatoid arthritis will lead to early treatment and therefore higher costs in the short-term (see Model 2). Therefore the cost savings identified in this model cannot be looked at, or generated, in isolation from the impact on treatment for people who are diagnosed early.

43 The extent to which resource utilisation incurred by non-IA UA patients in the current setting has a major impact on the cost modelled here. We assumed that people with undifferentiated arthritis currently visit their GP only once, have 50 per cent probability of being referred to specialists, and have a 50 per cent probability of undergoing the laboratory tests requested for IA patients. However, we assumed that those patients only incur one GP consultation. Although we carried out sensitivity analyses to test the impact of this assumption, further research is needed to examine the resource utilisation patterns of these patients.

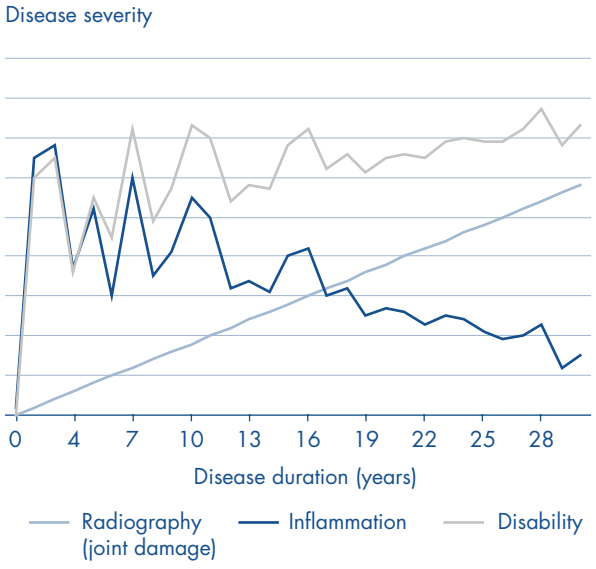
44 The model did not take account of the personal costs incurred by rheumatoid arthritis patients as a result of repeated visits and time taken for undergoing different diagnostic tests; hence it underestimates the true benefits of an EAC approach.

Model Two: Treatment of early rheumatoid arthritis

45 Rheumatoid arthritis is an inflammatory disease leading to joint destruction, loss of function and reduced quality of life[10]. Its cause is unknown but the process that leads to joint destruction appears to begin at the very onset of the disease[11]. Although there is no known cure for rheumatoid arthritis, early treatment offers an opportunity to limit or even arrest the irreversible damage that can take place where treatment is delayed. Early suppression of disease activity (inflammation) is essential for limiting joint damage and maintenance of work capacity in patients with recent-onset rheumatoid arthritis (Pulolakka K et al., 2005)[12]. Further still, the effects and responsiveness of treatment with conventional Disease-Modifying Anti-Rheumatic Drugs (DMARDs) decline with duration of rheumatoid arthritis, as demonstrated by Nell V et al. (2004)[13]. This model explores the impact of very early treatment (within three months of symptom onset) of people with rheumatoid arthritis on costs to the NHS, on productivity and on quality of life for people with the disease. **Figure 10** illustrates, for a typical person with rheumatoid arthritis, the progression of inflammation, joint damage and functional disability and the impact of early control of inflammation on the progression of joint damage.

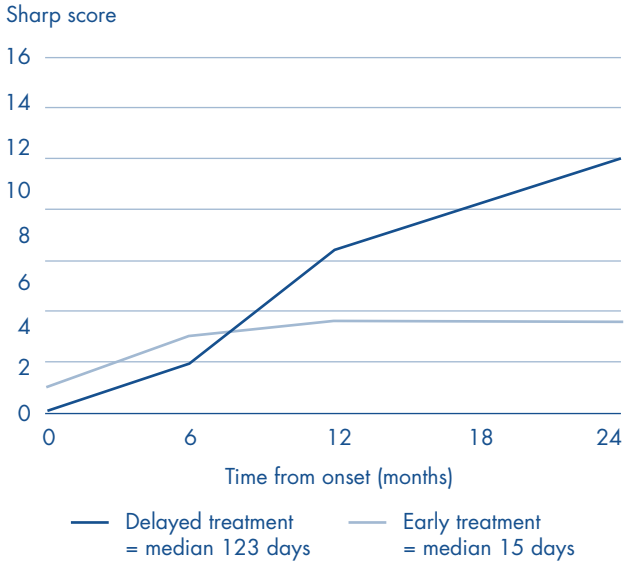
10 Disease progression and impact of the early treatment of rheumatoid arthritis compared to delayed treatment

Figure illustrates that disability at the very early stage of RA is mainly due to inflammation and as disease progresses, joint damage is increasingly linked to disability.



Source: Adapted from Kirwan et al. (2001)[1]

Sharp score is a measure of radiographic outcome/ progression on joints.



Source: Lard LR, Visser H, Speyer I, et al. (2001)[2]

NOTES

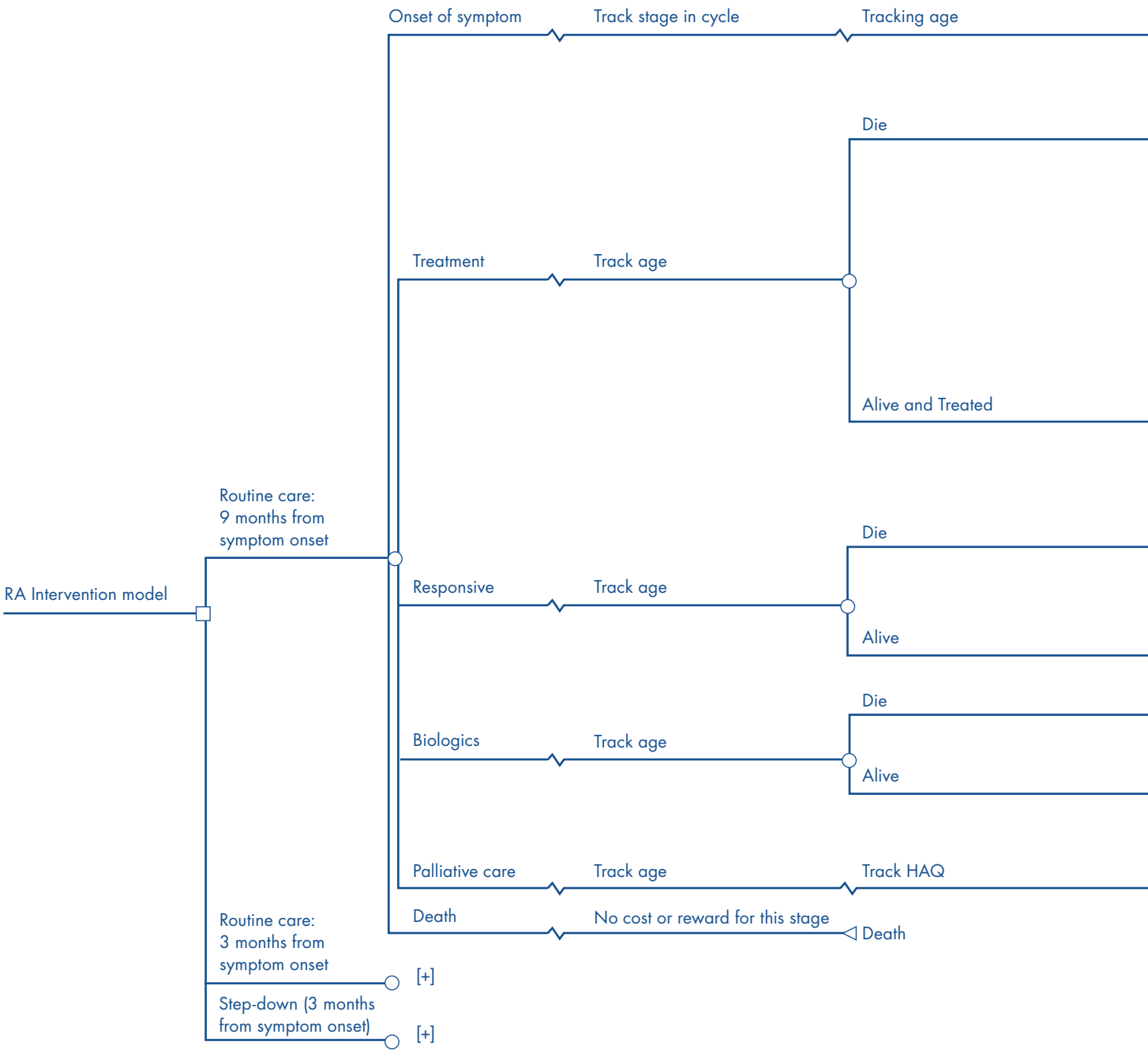
1 Kirwan JR et al. (2001) Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol. 2001 Apr;28(4):881-6.

2 Lard LR et al. (2001) Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med.* 2001;111:446-451.

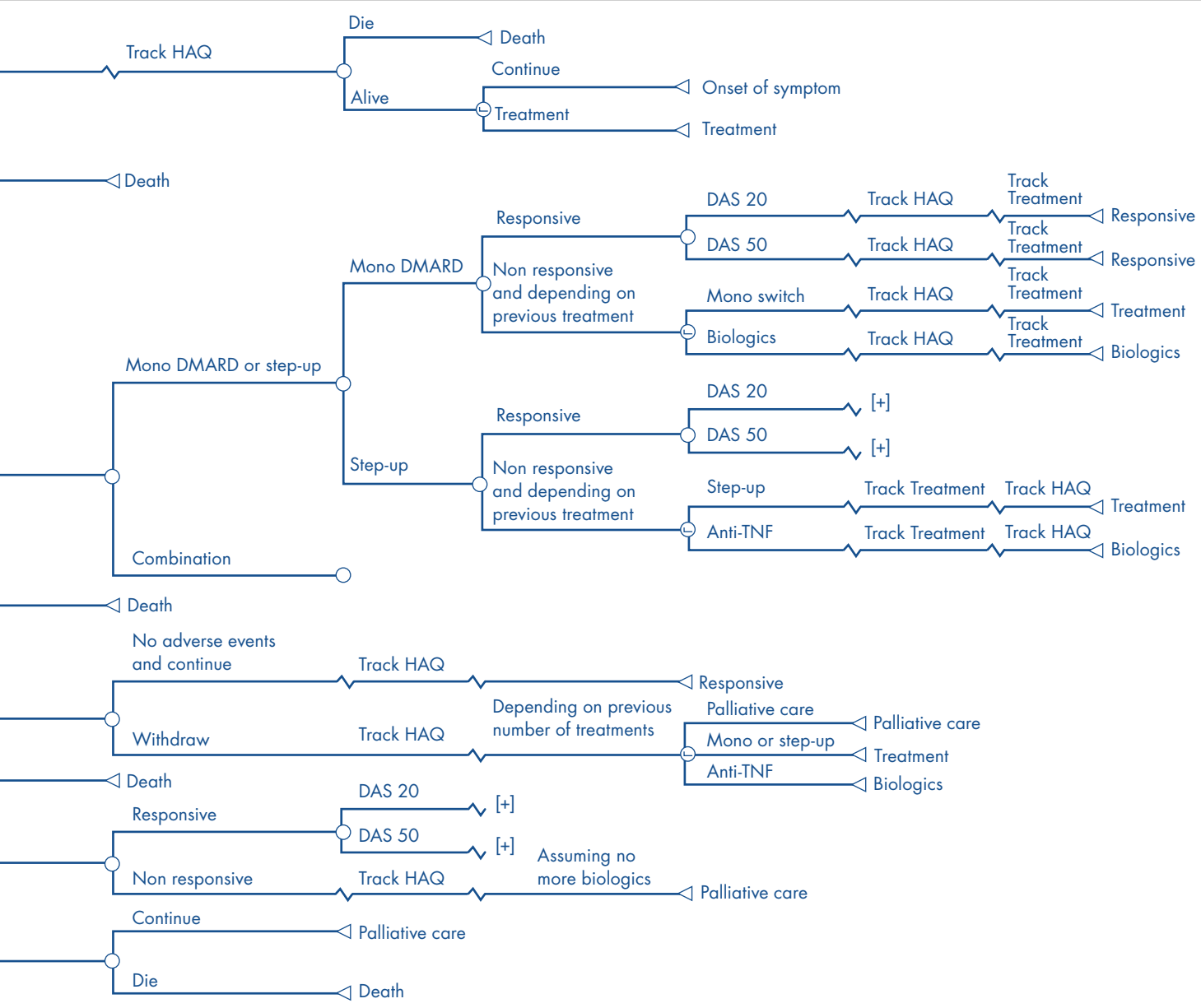
The model

46 The model is a discreet event simulation model constructed using the software package TreeAge 2008 Professional. **Figure 11** shows the model structure:

11 Decision tree model to examine the impact of early treatment of people with rheumatoid arthritis on costs to the NHS, on productivity and on quality of life for people with the disease

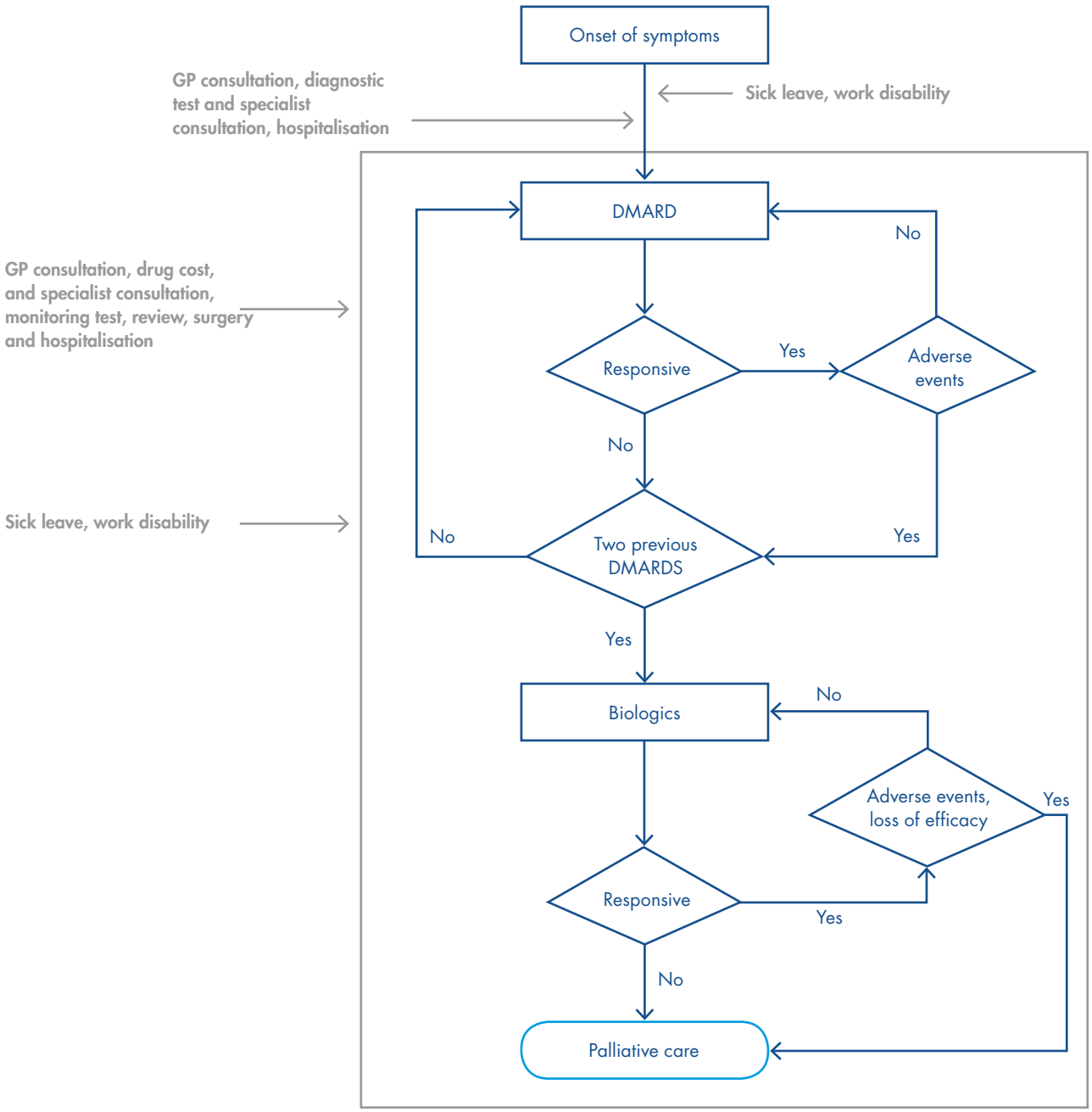


Source: National Audit Office


Track HAQ
Die
Death
Alive
Continue
Onset of symptom
Treatment
Treatment
Death
Mono DMARD or step-up
Mono DMARD
Responsive
Non responsive and depending on previous treatment
DAS 20
Track HAQ
Track Treatment
Responsive
DAS 50
Track HAQ
Track Treatment
Responsive
Mono switch
Track HAQ
Track Treatment
Treatment
Biologics
Track HAQ
Track Treatment
Biologics
Step-up
Responsive
DAS 20
[+]
DAS 50
[+]
Non responsive and depending on previous treatment
Step-up
Track Treatment
Track HAQ
Treatment
Anti-TNF
Track Treatment
Track HAQ
Biologics
Combination
Death
No adverse events and continue
Track HAQ
Responsive
Withdraw
Track HAQ
Depending on previous number of treatments
Palliative care
Palliative care
Mono or step-up
Treatment
Anti-TNF
Biologics
Death
Responsive
DAS 20
[+]
DAS 50
[+]
Non responsive
Track HAQ
Assuming no more biologics
Palliative care
Continue
Palliative care
Die
Death

47 The model simulates a patient pathway at an individual level (age, gender, initial HAQ[f]), from onset of symptoms to combination treatment with conventional DMARDs, then to biologics and ultimately to palliative treatment if the patient is not responsive to any intervention. It evaluates the cost incurred to the NHS (such as drugs, consultations and surgery) under three different scenarios of early rheumatoid arthritis management. The model terminates when a patient reaches the end of the evaluation period or if a patient has died during the timescale covered by the model. **Figure 12** shows the patient pathway simulated by the model.

12 Early rheumatoid arthritis treatment pathway and the resource utilisation simulated by the model



Source: National Audit Office

f HAQ (Health Assessment Questionnaire) is the most often reported patient reported RA outcome measure; its score is between 0-3. The higher the HAQ score, the worse the disease status.

48 The output of the simulation model is for an average patient over a five year period. The base case result is then applied to ten per cent of the annual incidence for five years (ten per cent is the proportion of people currently diagnosed within three months of symptom onset; see paragraph 19).

49 We have assumed that treatment begins promptly after diagnosis. The model simulates the following three treatment regimes (scenarios):

- **nine months with routine treatment** (scenario 1): Defined as starting treatment at nine months from onset of symptoms with routine sequential DMARD sequence initially (nine months is the median time from onset of symptoms to first treatment)[14]. After two failed DMARDs, a biologic is administered, if the patient fails to respond, then palliative care will be applied.
- **three months with early routine treatment** (scenario 2): Defined as starting DMARD treatment at three months from symptom onset, with the same sequence as above.
- **Step-down at three months** (scenario 3): Defined as starting first line treatment at three months using a combination of therapies, followed by a scale down to a more limited combination. If the patient is not responsive after six months of treatment, then they are treated with biologics. The NICE 2009 guideline recommends the step-down approach as the default strategy unless clinically contraindicated.[15] This option is included here to evaluate the potential impact of full adoption of the NICE approach.

50 People with rheumatoid arthritis commonly experience functional loss that translates into reduced productivity and work disability. For these three scenarios we therefore evaluated the following:

(i) Costs to the NHS. These are analysed for all patients regardless of their onset age. The following costs were included in the model:

- Drug costs (including administration and monitoring costs);
- Other NHS resource utilisation (hospitalisation, outpatient visits, joint replacement; we also considered physiotherapy and hydrotherapy in the sensitivity analysis);

(ii) The productivity impact on the economy. These are only included in the subgroup analyses for the working age population (the gains or losses are turned into a monetary value by applying the weighted national average wage):

- Lost employment (early retirement due to rheumatoid arthritis); and
- Sick leave.

(iii) Quality of life impact as measured by incremental Quality Adjusted Life Years (QALY)[g] (the measurement approach used by NICE). Although QALY measures both quantity and quality of life, in this analysis, we in effect compared the same patient with the same mortality. So, the gain or loss in QALY is equivalent to a gain or loss in quality of life. This outcome is analysed for all patients regardless of their onset age.

Health Assessment Questionnaire (HAQ) – The driver of the model

51 The model simulates the progression in HAQ (Health Assessment Questionnaire) score of each patient. HAQ is a well established measure for the overall well-being and functional mobility of people with rheumatoid arthritis. It is the most commonly referenced patient reported rheumatoid arthritis outcome measure. It is scored between 0 and 3, and the higher the HAQ score, the worse the disease status, from 0 requiring no need of assistance whilst 3 indicates a level of disability which requires significant personal assistance and devices to aid mobility and function. The initial HAQ is simulated from the distribution obtained from ERAN data (see paragraph 55).

g QALY: A composite measure for both quantity and quality of life, it is derived by weighing a year of life using utility values elicited from patients concerned or the general public.

52 We have made assumptions in the model, from literature review, about the impact of treatment on HAQ score (from treatment with DMARDs and biologics). Studies have shown that for people with rheumatoid arthritis, cost and quality of life are more closely correlated to HAQ score than to clinical outcome measures.[16, 17] The higher the HAQ score for the patient, the higher the cost to the NHS. In the model, patients are assigned to a discreet level of cost to the NHS if the simulated HAQ score falls into a certain HAQ band (illustrated in **Figure 13**).

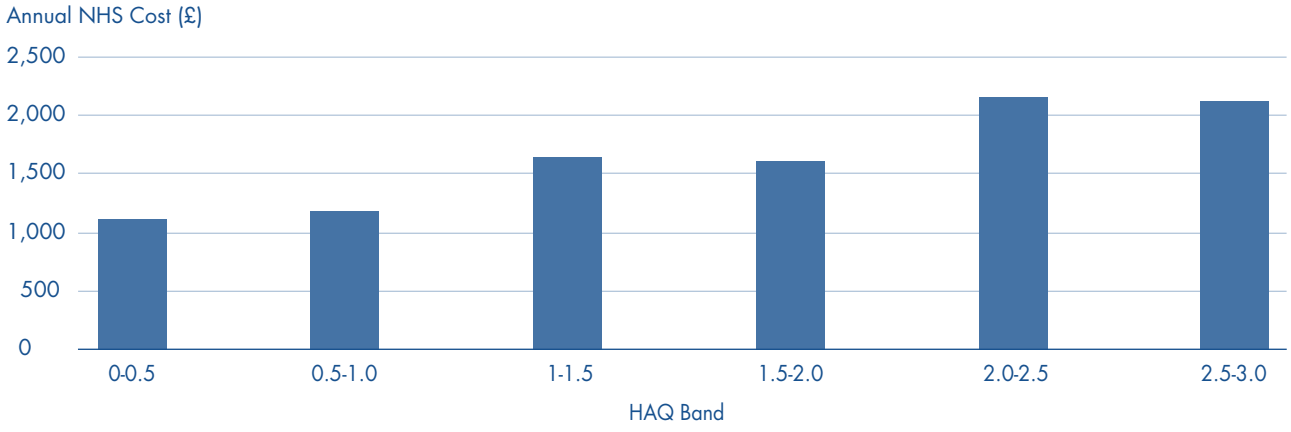
HAQ score and productivity

53 The impact on productivity loss including employment and sick leave are estimated according to the HAQ score, drawing on a range of literature and analysis of ERAN data.

HAQ score and quality of life

54 The patient's quality of life is also estimated according to HAQ **(Figure 14)**. We have evaluated Quality Adjusted Life Years (QALYs) arising from the model to analyse the cost effectiveness of the alternative treatment regimes. QALY is calculated by multiplying a year of life with a utility score for patients Health Related Quality of Life (HRQoL). Here the utility score is mapped according to patient HAQ score. Mapping from the HAQ score is an appropriate way to estimate a patient's utility score (NICE, 2009). For this model the values used were based on a regression analysis of US National Databank for Rheumatic Diseases which mapped HAQ to EQ5D[h] utility score[18] (Figure 14).

13 HAQ score and NHS resource utilisation[1]



Source: Taylor M et al. (2008) The Relationship Between Health Assessment Questionnaire Score And Resource Use In The Management Of Rheumatoid Arthritis. Poster Presentation. European League against Rheumatism Annual Conference. Paris, France, June 2008.

14 HAQ index and Utility

HAQ Index	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.25	2.5	2.75
Value	0.857	0.803	0.762	0.713	0.657	0.590	0.511	0.427	0.333	0.229	0.120	0.034

Source: NICE (2009) Rheumatoid CG79 Rheumatoid arthritis: full guideline appendices

h EQ-5D: EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys.

Baseline patient characteristics

55 Baseline patient characteristics have been obtained from the Early Rheumatoid Arthritis Network (ERAN) **(Figures 15, 16 and 17)**. The age specific mortality rate is from UK national statistics[19]. The probabilities on efficacy in the model are based on data from clinical trials which may differ from these baseline characteristics. We considered, however, it appropriate to use these data as there is no clinical evidence suggesting a difference in treatment effectiveness between patients with different baseline characteristics (NICE, 2009[20]).

15 Basic characteristics of the population of people with rheumatoid arthritis used in the simulation model (at 3 months from symptom onset for all patients)

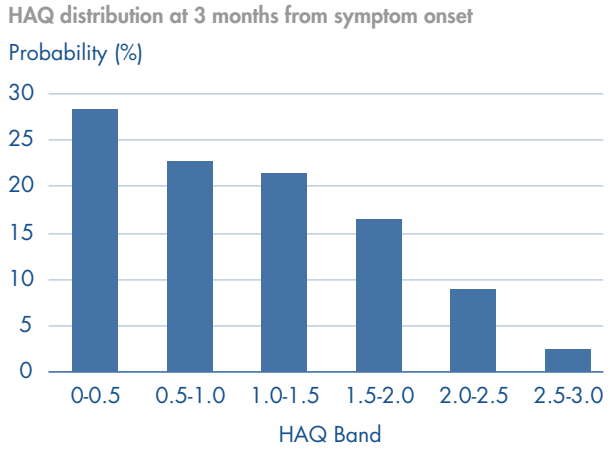
Parameter[1]	Value	SD
Average age of onset (non-normal distribution)	56.6 years (median 52 years)	14.1 years
Sex (females as proportion of total rheumatoid arthritis population)	66.6%	
Average HAQ score at three months from onset of symptoms	1.09	0.74

Source: ERAN

NOTE

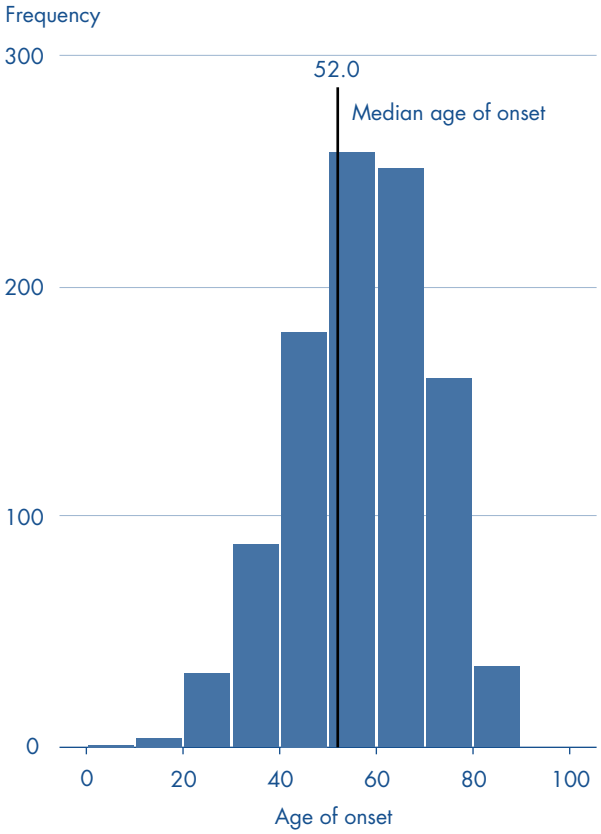
1 All are non-normal distributions, for comparisons to other cohorts used in literature.

16 Baseline HAQ score



Source: ERAN

17 Baseline distribution of age of onset from ERAN



Source: ERAN

NOTE

Mean =56.6

Std. Dev. =14.1

N =1,009

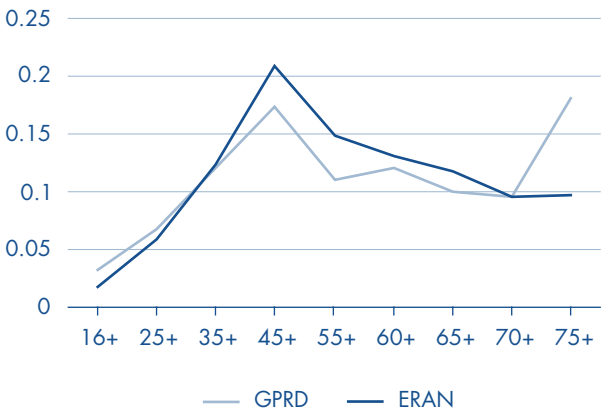
56 The appropriateness of the baseline characteristics obtained from the ERAN cohort as a representative sample of people with early rheumatoid arthritis in England has been demonstrated in **Figures 18 and 19**. For the working age population, Figure 18 shows that the distribution of onset age between GPRD and ERAN datasets is almost identical, with the exception of the incidence rate for the population over the age of 75, where the GPRD incidence rate is higher. Figure 19 shows the adjusted age distribution we used in the model (by doubling the proportion of new onset patients over the age of 75), these adjusted data were then used to estimate costs to the NHS.

Parameters on efficacy of conventional Disease-Modifying Anti-Rheumatic Drugs (DMARD)

57 **Figure 20** sets out the probabilities that have been used in the model and their sources. Probabilities on efficacy of DMARDs have been taken from NICE guideline meta-analysis where possible; otherwise they have been obtained from published literature. The efficacies for the treatment strategies used are the weighted averages for strategies estimated by NICE (2009).

58 Patients may withdraw from treatment due to adverse events (such as infection or pneumonia) or losses of efficacy. Both of these are included in the calculation for withdrawal rates from treatment. Withdrawal rates used are the weighted average of the patients withdrawal from each treatment regime as estimated from meta analysis of clinical trials by NICE (2009).

18 A comparison of distribution of age of onset between ERAN and GPRD

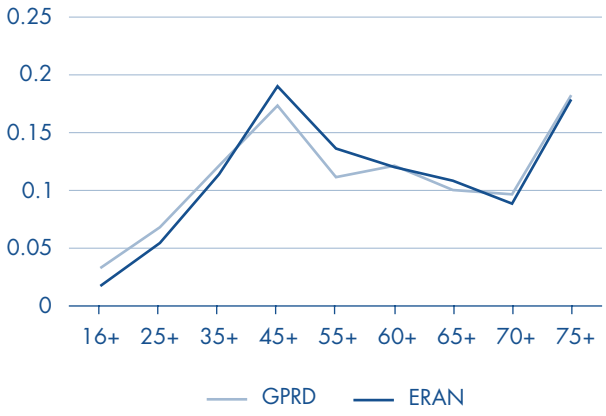


Source: GPRD and ERAN

NOTE

75+ includes all patients over the age of 75 rather than just for those aged between 75 and 84.

19 A comparison of distribution of age of onset between ERAN (adjusted) and GPRD



Source: GPRD and ERAN

NOTE

75+ includes all patients over the age of 75 rather than just for those aged between 75 and 84.

20 Probabilities for efficacy, rate of HAQ progression, and withdrawal rate for different DMARD treatment strategies

Efficacy

Response rate (after 9 months)	ACR20	ACR50	Source
Single DMARD – mono therapy	0.502	0.315	
Step-up	0.502	0.25	
Step-down	0.73	0.54	
Biologics (after two DMARD)	0.71	0.36	NICE (2009)[1]
Response rate (after 3 months)			
Mono DMARD (MTX – methotrexate) in very early rheumatoid arthritis	0.57	0.39	Breedveld FC et al. (2006)[2] E.William St. Clair et al. (2004)[3] Quin et al. (2005)[4] Bathon JM et al. (2000)[5] Aletaha D et al. (2008)[6]

HAQ Progression	Sub ACR20	ACR20	ACR50	Wailoo AJ et al. (2009 HAQ)[7]
Decrease in HAQ score for different ACR responses	-6.6%	37.8%	85.3%	NICE (2009)
Annual increase in HAQ after initial response	0.0418 (annual rate)			NICE (2009), Brennan et al. (2007)[8]
HAQ progression before treatment	0.100 (0.01-0.15) (annual rate)			Konnopka A et al. (2008)[9]

Withdrawal rates	6 month withdrawal rate	
Mono therapy	0.095	NICE (2009)[10]
Step-up	0.02	
Step-down	0.026	
Biologics	0.0415	Brennan et al. (2007)

NOTES

1 NICE (2009) Rheumatoid Arthritis National clinical guideline for management and treatment in adults (2009). www.nice.org.uk/guidance/index.jsp?action=folder&o=43336.

2 Breedveld FC et al. (2006) The premier study. Arthritis & Rheumatism Vol. 54, No. 1 Jan 2006, pp 26-37.

3 E.William St Clair et al. (2004) Combination of Infliximab and Methotrexate Therapy for early Rheumatoid Arthritis. Arthritis & Rheumatism Vol 50, No. 11, Nov 2004, pp 3432-3443.

4 Quinn MA et al. (2005) Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:27–35.

5 Bathon JM et al. (2000) Comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586–93.

6 Aletaha D et al. (2008) Arthritis: a pooled analysis of clinical trial results function varies with duration of rheumatoid. *Ann Rheum Dis* 2008;67;238-243.

7 Wailoo AJ et al. (2008) Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. *Arthritis & Rheumatism*. 2008; 58(4):939-946.

8 Brennan A et al. (2007) Modelling the cost-effectiveness of TNF_a antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology 2007;46:1345–1354.

9 Konnopka A et al. (2008) Cost effectiveness of the determination of auto antibodies against cyclic citrullinated peptide in the early diagnosis of rheumatoid arthritis. Annals of the Rheumatic Diseases 2008;67:1399-1405.

10 NICE (2009) Rheumatoid Arthritis National clinical guideline for management and treatment in adults (2009). www.nice.org.uk/guidance/index.jsp?action=folder&o=43336.

11 ACR 20 is a 20 per cent improvement in disease activity, whilst ACR 50 is a 50 per cent improvement in disease activity, according to the American College of Rheumatology criteria.

59 The effectiveness of DMARD treatments declines with the duration of rheumatoid arthritis[21] **(Figure 21)**. The model accounted for some of this effect by applying a higher response rate for patients starting on DMARD treatment at three months, obtained from meta-analysis of clinical trials (Figure 20, row 5).

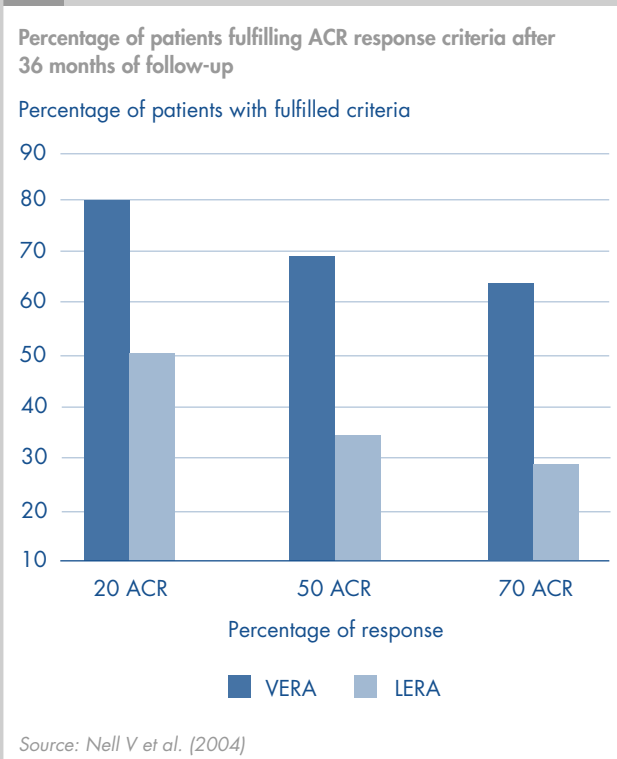
NHS resource allocation

60 NHS resource utilisation was closely correlated with disease severity and was estimated according to the HAQ score. We grouped by HAQ level the average usage of NHS resources by people with rheumatoid arthritis including hospital days; outpatient visits and surgery **(see Figure 22)**. NICE (2009) estimated the relationship between HAQ and NHS costs based on NOAR (for which most of the patients audited are within the first five years of disease onset), and we used this in our base case analysis.

61 In our sensitivity analysis we used data from an audit of NHS resource utilisation covering patients with an average disease duration of over ten years in order to capture the effect on longer-term costs. This audit was based in Hayward Hospital, Stoke on Trent, between 2002 and 2005 and included costs such as hydrotherapy and physiotherapy, with all patients followed prospectively (Taylor M, 2008).

62 Drug costs for different strategies are the weighted average for an average patient under each treatment regime (Figure 22). We took these from estimates in the NICE 2009 guidelines[22]. These costs are based on standard dosage and monitoring as set out in clinical trials reviewed by NICE in developing their economic model for the guideline, again those patients included in the clinical trials reviewed by NICE are mostly early rheumatoid arthritis patients. For biologics, we used the weighted average cost estimated by Brennan (2007) from the British Society for Rheumatology Biologics Registry. For biologics, because initial doses are higher and more frequent, we applied a higher initial cost for the first six months. For all other regimes, we assumed that cost between different periods does not change and a flat rate was applied for all consecutive periods of DMARD treatment.

21 The efficacy of DMARD for patients treated very early (within three months) compared to late treatment of early rheumatoid arthritis (more than three months but less than 12 months)



Source: Nell V et al. (2004)

NOTE

VERA: Very early RA. LERA: Late early RA.

22 Cost and rate of resource utilisation used in the model (2008 prices)

HAQ	NHS cost other than drugs per annum (£)	Source
0	120.23	NICE (2009)[1]
1	261.78	
2	579.94	
3	1,673.41	
0.0 to 0.5	1,112	Taylor M et al. (2008)[2] (only used in the sensitivity analyses)
0.5 to 1.0	1,179	
1.0 to 1.5	1,647	
1.5 to 2.0	1,602	
2.0 to 2.5	2,151	
2.5 to 3.0	2,121	
Weighted average six month drug cost		
Mono DMARD	251.40	NICE (2009)
Step-up	266.93	NICE (2009)
Step-down	269.29	NICE (2009)
Biologics	7998(1st)/6541 (2nd and after)	Brennan et al. (2007)[3] Inflated with CPI-health index

NOTES

1 NICE (2009) Rheumatoid CG79 Rheumatoid arthritis: full guideline appendices. www.nice.org.uk/guidance/index.jsp?action=folder&o=43336.

2 Taylor M et al. (2008) The Relationship Between Health Assessment Questionnaire Score And Resource Use In The Management Of Rheumatoid Arthritis. Poster Presentation. European League against Rheumatism Annual Conference. Paris, France, June 2008.

3 Brennan A et al. (2007) Modelling the cost-effectiveness of TNF_a antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology 2007;46:1345-1354.

Assumptions

63 Overall the assumptions made in the model are conservative, to minimise the risk of overstating the effects of the parameters within the model. The main assumptions in our second model are:

Assumptions about costs

(i) For the first three months from disease onset, the non drug costs to the NHS are 50 per cent of the average cost for each HAQ band.

Assumptions about treatment regimes

(ii) Patients diagnosed with rheumatoid arthritis are treated with one of the possible regimes; changes to treatment are made according to the response. (See Figure 12). We assume that treatment begins promptly after diagnosis. If a patient has an adequate response (ACR 20 or ACR 50[i]), he or she stays on the DMARD[j]. If there is not an adequate response, or withdrawal due to adverse reactions or loss of efficacy, this triggers a change of treatment.

(iii) After any two failed DMARDs, rheumatoid arthritis patients will be treated with biologics[k], which is the treatment pattern recommended by NICE. If not responsive to biologics, the patient will then be on palliative treatment (no second line biologics).

Assumptions about HAQ progression

(iv) Without any treatment HAQ score progresses at annual rate of 0.1. We made this assumption from a review of the literature.[23]

(v) If a rheumatoid arthritis patient withdraws from treatment either due to adverse events or loss of efficacy, all HAQ gains whilst on treatment are lost and patients revert back to their HAQ score before the corresponding treatment.

(vi) There is no impact on HAQ score during the first six months of treatment. In terms of treatment, it normally takes around three months for DMARD treatment to become effective, but to be conservative we have assumed there is no impact on HAQ until after six months on DMARD treatment. If there is an ACR 20 or ACR 50 response, we assume these lead to a one-off reduction in respective HAQ scores of 37.8 per cent and 85.3 per cent (NICE, 2009); if there is a sub ACR 20 response, we assume the HAQ score increases by 6.6 per cent. [24] After the initial response, we assumed an annual progression of 0.0418 in HAQ score for all treatment regimes except for those on biologics, where progression is assumed to be zero (Brennan et al, 2007).

Assumptions about mortality

(vii) Standardised mortality in people with rheumatoid arthritis is 1.3 times higher than in the general population. Within this, the model simulated mortality based on age and gender specific risk-adjusted mortality data. Sokka T et al. (2008)[25] reviewed literature on rheumatoid arthritis mortality, and reported that standardised mortality rates in patients with rheumatoid arthritis are 1.5-1.6 times higher than in the general population, with 1.2-1.3 in inception (new onset) cohorts and 1.6-1.7 in non-inception cohorts.

(viii) If an individual dies at any stage, they leave the model, applying the approach to mortality above.

Assumptions about productivity

(ix) Each person with rheumatoid arthritis in employment earns the equivalent of the national average wage. Using Office for National Statistics estimates, the average wage for the population as a whole was estimated to be £23,585 for 2007-08. The average wages for male and female workers at employment age were weighted according to the proportion of male and female rheumatoid arthritis patients (1:2) of working age, to account for rheumatoid arthritis disproportionately affecting working age women. The average working days in the model was derived from the weighted average wage and weighted average hourly rate for 2007-08, assuming an eight hour working day. **Figure 23** shows the results.

23 Average wage and average working days calculation

	Male	Female	Weighted
Gross wages average (2007-2008, £)	32,838	18,958	23,585
Hourly rate (£)	15	12	13
Average days worked per year	269	196	220

Source: Office for National Statistics[1]

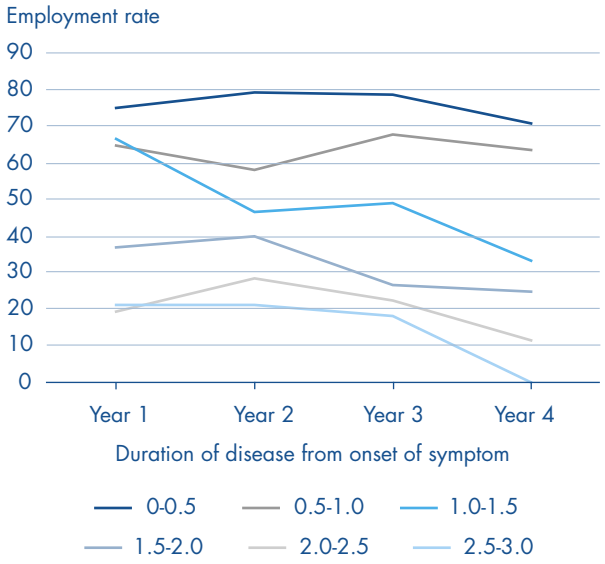
NOTE

1 Office for National Statistics (ONS) (2009) 2008 Annual Survey of hours and Earnings. www.statistics.gov.uk/StatBase/Product.asp?vlnk=15187.

i ACR 20 (ACR 50) is 20% (or 50%) improvement in disease activity according to the American College of Rheumatology criteria.
j DMARD disease-modifying anti-rheumatic drugs (DMARDs) is a category of otherwise unrelated drugs defined by their use in rheumatoid arthritis to slow down disease progression, such as Methotrexate (MTX).
k Drugs which can reduce joint inflammation in people with rheumatoid arthritis by targeting the individual molecules which cause inflammation and damage in joints.

(x) The effects of rheumatoid arthritis on a person's ability to work are closely correlated to HAQ score. Kobelt et al (2008)[26] reported the work participation for RA patients according to their HAQ score (Figure 25). We also analysed the employment loss according to HAQ score estimated from ERAN (2002-2008) **(Figures 24 and 25)**. Figure 24 shows that whilst there is hardly any change in employment rate for those with a HAQ score under 1 over the four year period from symptom onset, employment rates have declined significantly over the same period for those with a HAQ score over 1.

24 HAQ band and employment in the ERAN cohort over four years from disease onset



Source: National Audit Office analysis of ERAN data

(xi) Lost productivity as a result of sick leave is assumed to be the same as lost productivity as a result of presenteeism (presenteeism is not included in the base case analysis). Clinical trials have observed that sick leave is closely correlated to HAQ score[27], and the productivity loss through presenteeism and sick leave is very similar **(Figure 26)**, although no studies have directly linked HAQ score with sick leave days. Using data from Zhang et al (2008), we have assumed that the lost productivity through sick leave is of the same magnitude as productivity lost due to presenteeism. The model predicts an average of four months sick leave over a five year period under routine care, which is significantly lower than reported by Burton et al. (2006), which found that mean days of sick leave per employed individual with rheumatoid arthritis ranged between 30 and 90 days per year in the first ten years[28]. This indicates that the model prediction for sick leave is conservative.

Other assumptions

(xii) Adverse events. DMARD treatment can cause serious side effects such as infection, allergic reactions and liver damage. We did not include the cost from adverse events directly in the cost calculation; however, as in the NICE (2009) model, the cost for adverse events and the corresponding impact on QALYs are reflected indirectly in the calculation of treatment withdrawal rate, and also reflected in the monitoring cost for drugs.

(xiii) Discounting. The evaluation period is for five years (and ten years for sensitivity analysis). No discount rate is applied in order to give a more realistic picture of the fiscal impact; accordingly neither is a discount rate applied to quality adjusted life years.

25 HAQ band and employment rate

HAQ band	0-0.5	0.5-1.0	1.0-1.5	1.5-2.0	2.0-2.5	2.5-3.0
Rate of employment (Kobelt et al (2008))[1]	0.74	0.60	0.48	0.24	0.16	0.13
Reduction in probability of employment Comparing to HAQ band of 0-0.5	0.00	0.19	0.35	0.68	0.78	0.82
Rate of employment (NAO analysis of ERAN Data)	0.75	0.68	0.59	0.41	0.37	0.22
Reduction in probability of employment Comparing to HAQ band of 0-0.5	0.00	0.11	0.22	0.46	0.51	0.71

Source: Kobelt et al.(2008) and NAO analysis of ERAN Data

NOTE

1 Kobelt G. et al. (2008) Disease status, costs and quality of life of patients with rheumatoid arthritis in France: The ECO-PR Study. Joint Bone Spine 75 (2008) 408-415.

Uncertainties

64 Deterministic one way sensitivity analyses were carried out on NHS resource utilisation to test the uncertainties in estimates of the parameters in the model. We also extended the duration of the model to ten years to test the longer-term impact on the NHS of early treatment.

65 We carried out Probabilistic Sensitivity Analysis (PSA) to examine the uncertainties in the estimates or assumptions of some parameters; this is done for the working age population only. PSA accounts for the joint effects of uncertainty in the parameters (not patient characteristics) used in the simulation model by assigning distributions to those parameters. We then ran a 'Monte Carlo' simulation for those parameters. For each simulation of those parameters, a set of parameters were chosen randomly according to the distribution assigned. The process was run 1,000 times. For each one of the 1,000 set of PSA parameters generated, a set of micro simulations was then run (10,000 times) based on the initial distribution for patients' characteristics (such as age, gender and HAQ score). The resultant 1,000 PSA simulations demonstrate the effects of the uncertainties of those parameters on the initial simulation. We ran PSA on the following parameters (see paragraph 75 for results) (all other parameters were held constant):

- Annual HAQ progression rates (normal distribution);
- The reduction in HAQ attributable to different ACR 20 or ACR 50 responses (beta); and
- Withdrawal rates (beta).

26 HAQ score and sick leave

HAQ index	Workdays lost due to presenteeism	Assuming similar patterns for sick leave
0	14.3	14.3
0.25	34.5	34.5
0.75	61.1	61.1
1.25	63.4	63.4

Source: Zhang et al. (2008) How is reduced performance at work (presenteeism) associated with measures of disease severity in patients with osteoarthritis and rheumatoid arthritis (RA). Annals of Rheumatic Disease 2008;67 (Suppl II):583.

NOTE

Workdays lost due to presenteeism is not included in the base case analysis, instead this estimate is used only for approximation of sick leave.

Baseline results

Cost to the NHS for an average patient over five years

66 We have run the model for a five year period, which delivers the baseline results shown in **Figure 27 overleaf**. The results show that treating patients earlier than current practice by any DMARD regime will increase costs to the NHS (Figure 27 column 2). On average, a patient treated in three months would increase the cost to the NHS by £0.9k over the five year period; if the patient were treated with the step-down regime, the cost could rise by up to £1.6k for the NHS.

Employment impact for an average patient of working age

67 Early treatment, however, would bring about a reduction in lost employment of 30 days over the five years for a person of working age. For a patient treated with the step-down strategy, there could be a reduction of 42 days over five years. Early treatment, therefore, could generate productivity gains for the economy (Figure 27 column 4).

Quality of life for an average patient over five years

68 The model suggests that earlier treatment would also lead to an improvement in patient quality of life. A patient treated in three months with routine treatment would see an improvement in quality of life of about 4 per cent (0.14/3.45) as measured by QALY, and by 5.5 per cent (0.19/3.45) if treated with the step-down strategy.

Total impact over a five year period if an additional ten per cent of patients are treated within three months of symptom onset as opposed to nine months

69 **Figure 28** shows that over a five year period, the costs to the NHS of treating an additional ten per cent of new patients each year (2,600) within three months (for example as derived from Model 1) would be around £11 million (column 6). For those of working age, this earlier treatment could deliver productivity gains for the economy of around £31 million due to reduced lost employment and reduced sick leave.

Sensitivity Analyses

70 We ran the model for five additional years to examine if earlier treatment (scenarios 2 and 3, see paragraph 49) could lead to direct cost savings to the NHS in the longer-term. However, since most of the parameters were taken from literature on early rheumatoid arthritis, this may underestimate the long-term impact on surgery such as joint replacement, which becomes more likely as the disease progresses. **Figure 29** shows that after around eight or nine years the step-down strategy (scenario 3) would result in a cost saving to the NHS. For those on routine treatment (scenario 2), however, the initial extra cost is not offset in this period under the assumptions made in the base case scenario.

27 Average patient costs over the first five years (cost including cost to NHS and monetised value of productivity gains/losses)

	Average cost to NHS over the first five years (£000)	Incremental cost to the NHS (£000)	Average Working days lost monetised (£000) (working days lost)	Incremental productivity gain monetised (£000) (working days gained)	QALYs over five years	Incremental QALYs
Scenario 1 Nine months	12.8 (drugs: 11.2 other: 1.6)	–	34.3 (320)	–	3.45	–
Scenario 2 Three months	13.7 (drugs: 12.4, other: 1.3)	0.9	31.1 (290)	3.2 (30)	3.59	0.14
Scenario 3 Three months step-down	14.4 (drugs: 13.6, other: 0.8)	1.6	29.8 (278)	4.5 (42)	3.64	0.19

Source: National Audit Office, based on results of 10,000 simulations

NOTES

1 Two different approaches have been used to generate the cost figures in this table and the £560m overall healthcare cost to the NHS shown in Figure 8 of the main report. The cost in this table is modelled according to HAQ progression and the assumptions made in the construction of the model (Paragraph 63), assuming care is provided according to a standard setting as set out in clinical trials; the objective is to provide a base case scenario to evaluate other treatment strategies. The £560m in the main report covers *all* patients with rheumatoid arthritis and is estimated by aggregating the cost for secondary care (from directly observed data sources for secondary care) and spending by primary care (extrapolation from GPRD and prevalence, incidence data); the objective is to estimate the overall annual expenditure by the NHS on rheumatoid arthritis services (new and existing cases).

2 The £12,800 average cost to the NHS in the base case scenario here is for an average patient over the first five year period from symptom onset. It has two main components: component 1 is based on NHS resource allocation which includes outpatients, hospitalisation and surgery including staff costs and amounts to £1,600 (12 per cent) (see Figure 22 and Para 60); and component 2 is the cost of drugs which includes monitoring costs and amounts to £11,200 (88 per cent) (see Figure 22 and Para 62). The high drug cost arises from the assumption that for an average patient, after two failed DMARDs, biologics would be administered (this gives a higher proportion of patients on biologics after five years than is currently observed in practice). The objective is to establish an average base case cost which then enables us to look at incremental costs and impacts/outcomes of different treatment scenarios. Those assumptions are held constant for all scenarios, and therefore the impact on incremental cost which is the main output of this model, is marginal. The limitations of the modelling approach mean that it has not been used to estimate annual NHS healthcare expenditure on rheumatoid arthritis in the main NAO report (see note 1).

3 All prices in the model are quoted in 2008 prices; no discount has been applied, so the results reflect the impact in today's price rather than the net present value.

4 The work days lost is for an average person of working age only. It includes both lost employment and sick leave over a five year period.

5 QALYs are the total QALY for an average patient over the first five year period.

28 Impact over a five year period of treating an additional ten per cent of people with rheumatoid arthritis within three months of symptom onset

	Cohort 1 (five years in model)	Cohort 2 (four years in model)	Cohort 3 (three years in model)	Cohort 4 (two years in model)	Cohort 5 (one year in model)	Total £m
Average incremental cost per person to the NHS (£000, rounded)	0.9	0.9	1	1.2	0.4	
10 per cent of annual incidence	2,600	2,600	2,600	2,600	2,600	
Incremental NHS cost for 2,600 extra patients treated in 3 months (£m) of onset	**2.3**	**2.3**	**2.6**	**3.1**	**1.1**	**11.4**
Average productivity gain per person for working age only (£000, rounded)	3.2	3.0	2.7	2.4	0.8	
Productivity gains for 2,600 extra patients (£m) of working age treated in 3 months of onset	**8.3**	**7.8**	**7.0**	**6.2**	**2.1**	**31.5**

Source: National Audit Office

NOTES

1 This table illustrates the impact for five cohorts of patients over a five year period for ten per cent of new RA patients annually (i.e. 2600) treated within three months rather than nine months of symptom onset.

2 The average cost per patient is from Figure 27. The step in incremental cost in cohort 5 (in their first year from disease onset) is due to the drug cost of earlier treatment, and for cohort 4 (in the second year) the earlier treatment with biologics for those starting treatment within three months who subsequently had two failed conventional DMARDs (biologics have a much higher cost) which in the model would begin for some patients in the second year.

3 The higher incremental impact on productivity in the first and second year is due to patients who are treated earlier having had rapid control of symptoms in particular inflammation which is the main cause of work disability for early RA (see Figure 10). The effect on work disability through limiting joint damage is reflected more in the long-term and the incremental effect is less significant in particular in the early period of the disease.

29 Cumulative cost (£000) to the NHS for an average patient over the period of 6-10 years from disease onset

Year	6	7	8	9	10
Scenario 1 Nine months	16.3	19.8	23.4	26.7	29.8
Scenario 2 Three months	17.2	20.8	24.2	27.5	30.7
Scenario 3 Step down (three months)	17.7	20.4	23.1	25.7	28.5

Source: National Audit Office

71 To test these results over ten years, we also used the NHS service utilisation data as mapped by Taylor M. (2008) to evaluate the impact of a change of service utilisation patterns on NHS cost (see paragraphs 60 and 61). This was a more recent estimate, and a study cohort with older age and longer duration of rheumatoid arthritis. We therefore used this for the 6-10 year periods only **(Figure 30)**. These results confirm the findings above; that the step-down approach is the most cost effective strategy.

72 As mentioned above (paragraph 59) the efficacy of DMARDs for people with very early rheumatoid arthritis is significantly higher than for patients with delayed treatment, with a higher response rate as well as a higher proportion of higher response. The model reflected this to some extent by applying a higher ACR20 and ACR50 response rate for early mono DMARD treatment. However, this response rate is estimated from clinical trials with patients with a mean duration of more than three months. Nell V et al. (2004) compared treatment within three months with those treated with a mean duration of one year. The improvement in response rate reported for very early treatment is much higher after three months of treatment (65 per cent ACR20 and 50 per cent ACR50 as opposed to 20 per cent ACR20 and 15 per cent ACR50 at the end of three months of treatment, an improvement in response rate of about 100 per cent; even at the end of 36 months of follow-up the improvement in response rate is over 30 per cent). This improvement is of much higher magnitude than those used in the base case analysis (from 50 per cent ACR20 to 58 per cent ACR20 for mono DMARD, no change in efficacy between very early and late treatment for all other treatment). A deterministic sensitivity analysis was performed to evaluate the impact of improved response to DMARD through very early treatment upon average costs to the NHS per patient with rheumatoid arthritis by assuming an improvement in efficacy of 5, 10, 15 and 20 per cent for very early treatment in three months. As can be seen in **Figure 31** opposite, if the improvement of responsiveness of very early treatment is as much as ten per cent, within five years the cost to the NHS could be neutral.

73 These sensitivity analyses explored the uncertainties around the long-term effect of earlier treatment, the uncertainties around the estimate of NHS resource utilisation (paragraph 70, 71) and the uncertainties of the efficacy of earlier treatment (paragraph 72) in the literature. These analyses suggest that although earlier treatment leads to an initial cost increase to the NHS due to increased drug utilisation and monitoring, there is evidence to indicate that it could become cost neutral to the NHS in the medium to long-term. Without assuming that earlier treatment does lead to significant improvement in response rate as demonstrated by Nell V et al.(2004), earlier treatment could become cost neutral to the NHS in around nine years with the step-down strategy; if an improvement of ten per cent in efficacy is assumed, under either scenario, it could become cost neutral to the NHS within five years of treatment. Furthermore, the model did not include potential savings to the NHS due to reduced carer, nursing home, and home adaptations costs through better disease control. Therefore, overall, under these scenarios, our analyses suggest that earlier treatment could become cost neutral after around nine years (or earlier); if NICE recommendations are adopted cost savings could be realised in the medium to long-term.

74 In the base case analysis, we used the employment loss based on Kobelt et al.(2008). The study is based on a larger database than ERAN; however, the study was a snapshot of all patients with rheumatoid arthritis with different duration in France, while ERAN is based in the UK and the data are based on inception patients from 2002-2008. We reran the analyses on productivity using estimates based on ERAN data. The result is reported in **Figure 32**. Based on ERAN, the productivity gain is about 20 per cent less than the estimate based on Kobelt et al. (2008). This difference could be attributed to sampling difference, or because the outlook for employment has improved in recent years for all patients with different disease severity, or because more people are now employed in the non-manual sector and thus less likely to lose employment earlier during the first few years of the disease (data from ERAS following patients up to 15 years show that people with rheumatoid arthritis in manual jobs are more likely to lose their job early on in the course of their disease, see **Figure 33 on page 36**.)

30 Cumulative cost (£000) to the NHS for an average patient (using cost estimates from Taylor et al (2008)) over the period of 6-10 years from symptom onset

Year	6	7	8	9	10
Scenario 1 Nine months	21.4	25.7	29.6	33.7	37.7
Scenario 2 Three months	22.2	26.5	30.7	34.8	38.7
Scenario 3 Step-down (three months)	23.5	26.7	30.3	33.8	36.7

Source: National Audit Office

31 Deterministic sensitivity analyses to evaluate the impact on average NHS costs per RA patient (£000) of improved efficacy of early treatment (over five years)

Improvement in efficacy	5%	10%	15%	20%
Scenario 1 Nine months	12.8	12.8	12.8	12.8
Scenario 2 Three months	13.3	12.8	12.2	11.8
Scenario 3 Step-down (three months)	13.9	12.8	11.7	10.5

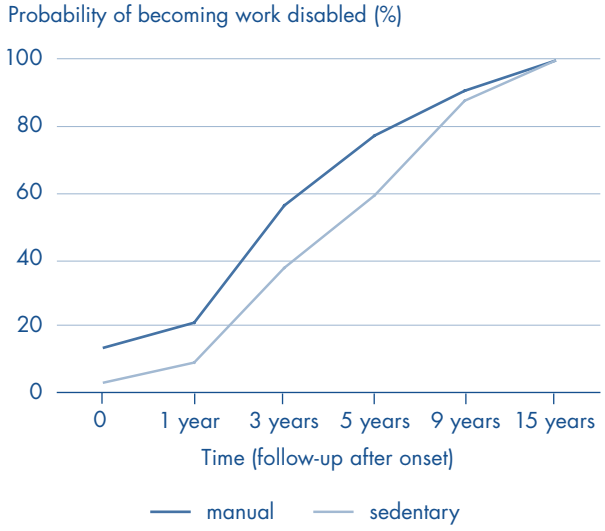
Source: National Audit Office

32 Deterministic sensitivity analyses to evaluate productivity loss per patient of working age (£000)

	Scenario 1 Nine months	Scenario 2 Three months	Scenario 3 Step down (three months)
Productivity loss (gains) based on ERAN data	26.7	24.1	23.4
Incremental change		(2.6)	(3.3)
Productivity loss (gains) based on Kobelt data	34.3	31.1	29.8
Incremental change		(3.2)	(4.5)

Source: National Audit Office

33 A comparison of the time to work disability for people with rheumatoid arthritis in manual and sedentary jobs who had become work disabled



Source: National Audit Office analysis of data from the Early Rheumatoid Arthritis Study (ERAS)[1]

NOTE

1 ERAS (Early Rheumatoid Arthritis Study) started in 1986 and has over 1,000 RA patients on its database. The ERAS centres cover different regions of England, including rural, urban and inner city communities. The data base contains information on differences in socio-economic effects and resource use on the outcomes of rheumatoid arthritis. The population shown here covers those who had become work disabled (15 years of follow-up).

75 **Figure 34** and **Figure 35** explore the joint effects on the results from the uncertainty over the parameters in **Figure 36** for the working age population only. Due to the lack of data on the distribution for those parameters, the distributions assigned are arbitrary while attempting to be realistic. Therefore, Figures 34 and 35 should be treated as exploratory rather than conclusive.

76 Figure 34 and Figure 35 show that, with all other parameters held constant, there is more than 99 per cent likelihood that, for the working age population, early treatment will generate productivity gains which outweigh the costs to the NHS.

Discussion

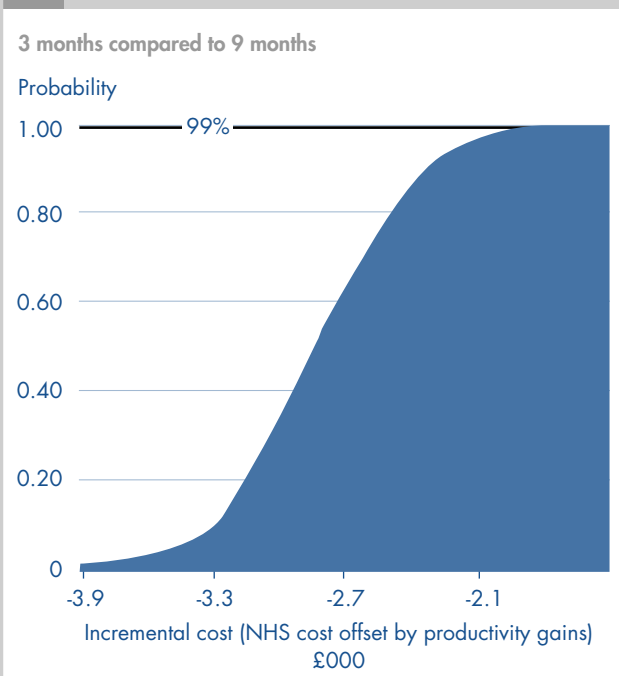
77 Rheumatoid arthritis is a chronic disease with an acute onset for most patients. Although there is no known cure, commencing treatment within three months of symptom onset offers the opportunity to minimise damage from the disease. Our second model shows that while early treatment of people with rheumatoid arthritis with recent onset of symptoms would lead to increased expenditure for the NHS in the short-term, in the longer-term savings to the NHS could be realised at least for those people with rheumatoid arthritis who have more aggressive treatment (the step-down approach recommended by NICE).

78 Many people with rheumatoid arthritis experience functional loss that translates into reduced productivity and work disability at very early stages of the disease. Up to 23 per cent of patients have become work disabled by one year after onset of symptoms[29], and one third of people with the disease will have stopped working within two years of onset[30]. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis (Pulolakka, 2005)[31]. Our model demonstrates that very early treatment of people with recent-onset rheumatoid arthritis could lead to significant productivity gains. Our model also demonstrates that a step-down (combination) strategy is more effective in reducing the negative impact on productivity; this is in line with findings from clinical trials **(see Figure 37)**.

79 Since rheumatoid arthritis has no known cure; the main objective of treatment is to improve quality of life for people with the disease. Our model has shown that earlier treatment could improve patients' quality of life by around four per cent over the first five years, as measured by QALYs.

80 With no change in routine use of DMARD, a patient treated within three months would increase the cost to the NHS by £900 over five years, with a gain in QALY of about 0.14, the cost effectiveness ratio is about £6,400 per QALY gained, which is within the cost effectiveness range applied by NICE, of £20,000-30,000 per QALY gained. If a step-down strategy is adopted, then the cost effectiveness ratio is £8,000 per QALY gained.

34 The PSA distribution for incremental cost (NHS cost offset by monetised productivity gains) for working age population treated in 3 months compared to in 9 months with routine treatment over the first five years

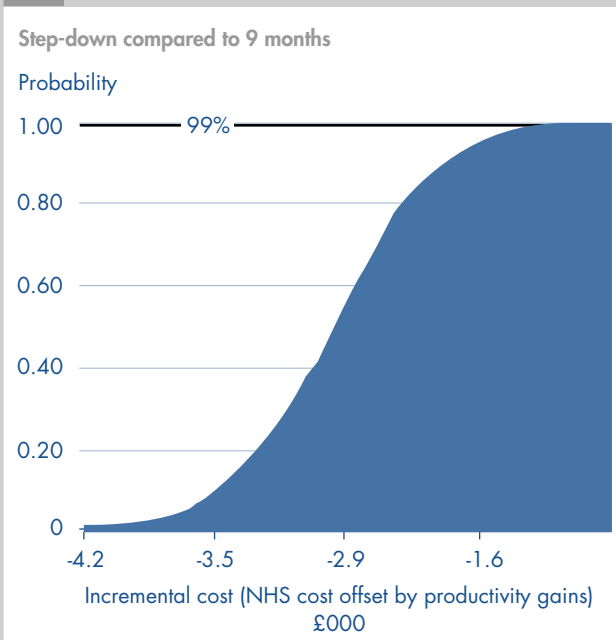


Source: National Audit Office

NOTE

The outcome here includes both costs to the NHS (drugs and other resource utilisation) and monetised productivity gains for the working age population.

35 The PSA distribution for incremental cost (NHS cost offset by monetised productivity gains) for working age population with step-down treatment in 3 months compared to routine treatment in 9 months over the first five years



Source: National Audit Office

NOTE

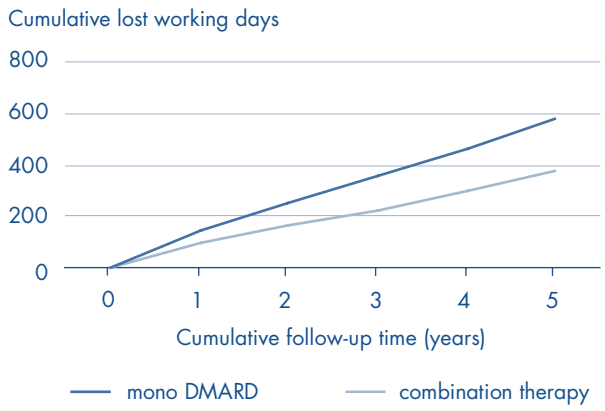
The outcome here includes both costs to the NHS (drugs and other resource utilisation) and monetised productivity gains for the working age population.

36 Distributions used for PSA and the parameters used for the distributions

	Distribution Type	Parameters
HAQ progression/reduction		
Annual HAQ progression rate before treatment	Normal	Mean 0.066, Sd: 0.01
HAQ reduction ACR 20 response	Beta	Alpha: 98.37 Beta: 161.87
HAQ reduction ACR 50 response	Beta	Alpha: 117.99 Beta: 20.33
HAQ increase Sub ACR 20 response	Beta	Alpha: 8.4 Beta: 131.6
Withdrawal rate		
Mono DMARD	Beta	n=1,000, r=95
Step-up strategy	Beta	n=1,000, r=20
Step-down strategy	Beta	n=1,000, r=26
Biologics	Beta	n=1,000, r=42

Source: National Audit Office

37 The impact of different treatment regimes on productivity loss



Source: Mottonen T, Hannonen P, Leirisalo-Repo M, et al. (1999)[1]

NOTE

1 Mottonen T et al. (1999) Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999;353: 1568-1573.

81 Increasing from 10 to 20 per cent the number of people treated within three months (ie an additional 2,600 patients each year) would initially increase overall NHS costs by £11 million over the first five years; but would improve people's quality of life and for the proportion that are of working age, earlier treatment would improve their chances of remaining in work, generating productivity gains for the economy of around £31 million. After around nine years, earlier treatment could become cost neutral to the NHS.

82 One way sensitivity analyses, sub group analyses and PSA sensitivity analyses have demonstrated that these findings would hold under a wide range of scenarios.

Conclusions

83 Our analyses have provided clear evidence that better value for money could be achieved by providing more rapid treatment for people with early onset rheumatoid arthritis. It could improve patients' quality of life and deliver productivity gains for the economy. Although it could increase the cost to the NHS in the short-term, it would be cost effective, and could be cost saving in the longer-term. The analyses also confirm the NICE conclusion that intensive early treatment with step-down strategy is more cost effective than current routine practice in terms of sequential DMARD treatment (which is dominated by mono switch treatment strategy), and suggest that potential cost savings to the NHS could be realised in the medium to long-term.

Limitations and caveats of the model

84 This is an evaluation of very early treatment of people with rheumatoid arthritis based on available evidence from literature reviews and other sources. It is intended to inform a value for money analysis of different treatment strategies for patients with recent onset of symptoms.

85 Parameters for the model are mostly based on studies for the first few years from disease onset; partly because very few studies have been carried out for populations beyond five years of onset. The basis for estimates over the longer period may therefore be of limited reliability; refinements could be made if there were more evidence on the impact of different treatment strategies in the longerterm. Due to the nature of disease progression, and the parameters used in the model, for longer disease duration, the model may underestimate the impact of early treatment on NHS resource utilisation due to surgery, outpatient visits and hospitalisation.

86 Various assumptions of the model were applied to simplify the care pathway of a person with rheumatoid arthritis. The model assumed that if a patient did not achieve an ACR20 or ACR50 response after six months, it would trigger a change of DMARD (step-up, mono switch to another DMARD, or biologics). These treatment assumptions, however, will not be clinically appropriate for all patients and individual treatment regimes will involve much more subtlety than we can simulate in a model. We also assumed that after two failed conventional DMARDs, a patient would be placed on biologics treatment, as per the NICE guideline. In practice, the period over which this takes place and the practice of moving to biologics, will vary.

87 The analyses here implicitly assume that all patients would accept DMARD treatment if clinically appropriate, and would adhere to treatment until loss of efficacy and adverse events, and that they will stay on treatment until the end of the model. In most cases, people will stay on treatment beyond the period covered by the model, if the treatment is effective for them. However, we have not reflected in the model circumstances where people may decline or stop treatment (i) due to concerns about side effects or (ii) because they choose to do so, or (iii) where they may not adhere to treatment as closely as patients in clinical trials.

88 The objective of the model is to enable us to look at incremental costs and impacts/outcomes of different treatment scenarios. The assumptions and simplifications made are held constant for all scenarios; therefore the impact on incremental cost is marginal. However, the total healthcare expenditure on rheumatoid arthritis derived from the model would be likely to be an overestimate whilst the total productivity loss would be likely to be underestimated.

89 The model simulates the HAQ progression under different scenarios. While HAQ is the best available instrument for this type of modelling, it may not be sensitive enough to capture all changes following different interventions. Resource utilisation and impact on productivity are modelled according to HAQ bands, although subtle changes within each band may not be reflected in the model.

90 Information on employment in particular on sick leave is derived indirectly. The model understates the impact of rheumatoid arthritis on work disability and sick leave compared to that reported by the literature. The model only considered the impact of rheumatoid arthritis on paid employment through early retirement and sick leave. This did not take account of those people who remain in work but have to reduce their working hours, nor did we consider the impact of presenteeism on productivity. More women than men are diagnosed with rheumatoid arthritis. We have, however, not considered the impact of rheumatoid arthritis on household productivity in this model. More research is needed to evaluate the impact of rheumatoid arthritis on employment and productivity.

91 The model only considered a representative scenario of routine practice, and the parameters used were weighted averages. This could be improved by considering individual sequential DMARD use; however this would require a much more complex model.

92 This model only looked at the direct cost arising from patients with rheumatoid arthritis; it did not take account of indirect costs such as carer costs or the impact on family members and the impact on their quality of life.

Endnotes

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