SECONDARY HEALTH SERVICE CARE AND SECOND LINE DRUG COSTS OF EARLY INFLAMMATORY ARTHRITIS IN NORFOLK:

by

Nicola Cooper[1], Miranda Mugford[1], David G.I. Scott[2].

School of Health Policy and Practice, University of East Anglia, Norwich. [2]Rheumatology Unit, Norfolk Arthritis Register, Norwich.

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Summary:

This paper reports the results of a retrospective longitudinal study designed to estimate the secondary health service care and second line drug costs (including drug monitoring costs) for a cohort of people with early inflammatory arthritis. The study population consisted of 344 people with inflammatory arthritis who had enrolled on the Norfolk Arthritis Register (NOAR) in 1990/91. Utilising data from the NOAR, augmented by data from other sources, the average (per person) and cumulative secondary care and second line drugs costs were estimated for years 1, 2, 3, 4 and 5 following a person's registration to NOAR (i.e. shortly after their onset of the arthritis). A logistic regression model showed the level of functional disability suffered by members of the study cohort and the presence of rheumatoid factor at registration to be positively related to the secondary health service care and second line drug costs they incurred; that is, people with the greatest disability and the presence of rheumatoid factor at registration incurred the highest costs over five years.

Introduction:

The economic burden of rheumatoid arthritis (RA) is thought to be substantial for both the person with the disease and the health services. Evidence from US-based studies have shown people with RA to face three times the cost of medical care, twice the rate of hospitalisation and four times the number of ambulatory visits to physicians than an age- and sex-matched non-arthritic population[1]. Findings suggest that the total and per capita lifetime economic costs of RA are similar to those incurred by stroke and coronary heart disease patients in the US[2]. There have been few studies (either practical or theoretical) on the costs of RA based in Europe[3-5].

In 1989 the community-based Norfolk Arthritis Register (NOAR) was set up with the primary aim of identifying and studying all the new cases of inflammatory arthritis, of which RA is a subset, in the former Norwich Health Authority via notification from general practitioners and hospital clinics. Since the register was established, approximately 350 people each year have agreed to take part in the project. Based on the NOAR data it can be estimated that there are approximately 22,700 new cases of inflammatory arthritis each year in the UK[6].

This paper reports the results of a retrospective longitudinal study to estimate the secondary health service care and second line drug costs for a cohort of people with early inflammatory arthritis from NOAR. Both the average (per person) and cumulative costs arising as a result of inflammatory arthritis at 1, 2, 3, 4 and 5 years following a person's registration to the project (i.e. closely after diagnosis of the disease) are calculated. Statistical analyses are performed to test for cost differences by socio-demographic and clinical characteristics.

The reason for this study, was not to inform choices about which treatment or therapy is the most cost-effective option for people with inflammatory arthritis, but to assist the decision-making process at policy and planning levels by identifying where the major burden of cost lies in the treatment and secondary care of these people. It also aimed to identify subgroups of people who are more likely to incur higher costs than other people.

The study reported in this paper is part of a larger project to investigate the direct and indirect costs of inflammatory arthritis in the first five years following onset. To date very few studies of this kind have been conducted in this area of rheumatology[7].

Methods:

Study population:

The study utilised data on the 433 people with early inflammatory arthritis, who registered with the NOAR project in 1990/91. These people were all adults (aged over 16) who fulfilled the following criteria:

a) swelling of two or more joints;

b) disease duration more than 4 weeks; and

c) disease onset after January 1989.

In particular, the study focused on the 344 people who either completed 5 years of follow-up (300 people) or died during the study period (44 people).

Resource use data sources:

The NOAR database provided annual health services use data, including the number of arthritis-related outpatient visits and inpatient stays; second line drug use start and stop dates; and steroid dosages. It also provided socio-demographic data (age, sex, smoking status, social class and ethnic group) and functional disability data measured by the Health Assessment Questionnaire (HAQ) and recorded annually. Information on the study subjects' length of stay in hospital (admission and discharge dates), where applicable, were extracted from either the hospital information system (HIS) or the hospital medical records.

GP guidance notes from the Rheumatology Unit at the Norfolk and Norwich NHS Trust, in conjunction with information extracted from the British National Formulary[1] (BNF), were used to provide a description of the 'typical' treatment regime[2] for each of the second line drugs and the laboratory tests required for drug monitoring. Second line drugs are defined as slow-acting anti-rheumatic drugs (SAARD), also known as disease-modifying and anti-

[1] BNF quotes basic net prices (exclusive of VAT) usually based on the largest pack size of preparation in use in community pharmacies. Costs to the NHS greater than net prices as include professional fees, overhead allowances and VAT.

rheumatic drugs (DMARD), which appear to have an affect on the underlying disease process[8] by arresting disease progression.

Unit costs data sources:

To supplement the resource-use data it was necessary to obtain unit costs for second line drugs, inpatient stays and outpatient visits. The average (net) cost per milligramme for each second line drug were obtained from the BNF. The unit costs for the numerous laboratory tests people with arthritis undergo to manage the toxicity of second line drugs, were obtained direct from the laboratories at the Norfolk and Norwich NHS Trust. Hospital charges (purchaser costs) for outpatient visits and inpatient stays, by hospital department (Rheumatology or Orthopaedic) were obtained from a local provider - the finance department at the Norfolk and Norwich NHS Trust[3] -and calculated by a standard top-down accounting approach.

A standard disease costing approach was adopted throughout the study by applying the following costing equation:

$$\sum_{i=1}^{n}\sum_{j=1}^{m} \textbf{(frequency)}_{ij} \, x \, \textbf{(unit cost}^{4}\textbf{)}_{j}$$

where i = *ith individual* ($i = 1,.....n$)

j = *jth service received* ($j = 1,.....m$)

(i.e. inpatient and outpatient care, and different second line drugs)

No discount rate was applied in the main analysis, although this could be done if the same data was to be used for the comparison of treatment options in the future.

Analysis:

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[2] 'Typical' treatment regime is defined as the daily dose consumed over time by the average person with RA seen by the GP or Rheumatologist.

[3] A minority of patients visited St. Michael's Hospital in Aylsham where no formal costing framework was available.

[4] The Hospital and Community Health Service (HCHS) pay and prices index[9] was used to express unit costs at constant 1990/91 prices.

Baseline analysis: A series of baseline analyses were conducted to test the null hypotheses that there were no statistically significant differences in socio-demographic characteristics of the study population (i.e. gender, age, social class, HAQ score, ethnic group, smoking status, and employment status) between i) registration years 1990 and 1991, and ii) completion of five years follow-up and part completion of five years follow-up either due to 'drop-out' or death during the study period.

Cost analysis: Retrospective estimates of the average (per person) and cumulative secondary health service care costs and second line drugs costs arising as a result of inflammatory arthritis at years 1 to 5 following a person's registration to the NOAR (i.e. closely after diagnosis of the disease) were calculated and summarised using the appropriate descriptive statistics.

The study population was stratified in terms of their age and HAQ scores at registration to NOAR, and cost differences between the groups tested. Age was categorised as less than 65 years and greater or equal to 65 years to represent those of employment age and retirement age respectively. The median value of the HAQ disability score recorded at registration was used as the cut-off between high and low disability. By stratifying the study population it allowed differences in the secondary health care costs and second line drug costs between the groups to be investigated.

Regression analysis: The study population was categorised as either high or low cost, according to their total five year cost. To determine which socio-demographic and clinical characteristics influenced a patient's cost category, forward stepwise logistic regression[9] was used to 'model' the relationship between high or low cost (the dependent variable), and a set of predictor/independent variables (socio-demographic and clinical characteristics). This replicated the approach used by van Jaarsveld et al 1998[5].

Sensitivity analysis: The sensitivity of the costs obtained in the main analysis to changes in the following variables were investigated.

- Second line drug costs - increased by 10% and 20% to make allowances for the omission of professional fees and overheads as well as management of side effects in problem cases.
- Secondary care costs - ±10% to make allowances for the imprecision of hospital price estimates plus the variations across hospitals.

Results:

Throughout the results section the median, together with the 2.5th and 97.5th centiles, have been quoted as the main summary statistics due to the positively skewed distribution of the cost data[10]. With asymmetrically distributed data, the mean cost and 95% confidence interval do not satisfactorily describe the range of the bulk of the data. Although the confidence interval would still include 95% of the observations, its use would result in implausible negative lower confidence limits, and the exclusion of observations all in one tail of the distribution. However, the mean and standard deviation are quoted in a number of the accompanying tables to allow comparisons to be made with other studies where the mean was the only summary statistic used.

Study population:

Out of the 433 people who registered on the NOAR database in 1990/91, 300 people (69%) completed the full 5 years of follow-up, 44 people (10%) died during the study period and 89 people (21%) either declined, were lost to follow-up or followed up by postal questionnaire[5] only.

The main analysis reported here focuses on the 344 people who either completed the five years of follow-up or died during the study period. For those people who died, data was only available up to the date of administration of the last NOAR follow-up.

Baseline characteristics and analysis:

[5] Postal questionnaire consists of a minimal number of questions. It includes the health assessment questionnaire but not sufficient data for use in this study.

Table 1 summarises the characteristics of the study population at registration to the NOAR project. The median delay in presentation to NOAR, following diagnosis of inflammatory arthritis, was 164.5 days (Interquartile range (IQR) of 86 to 340 days).

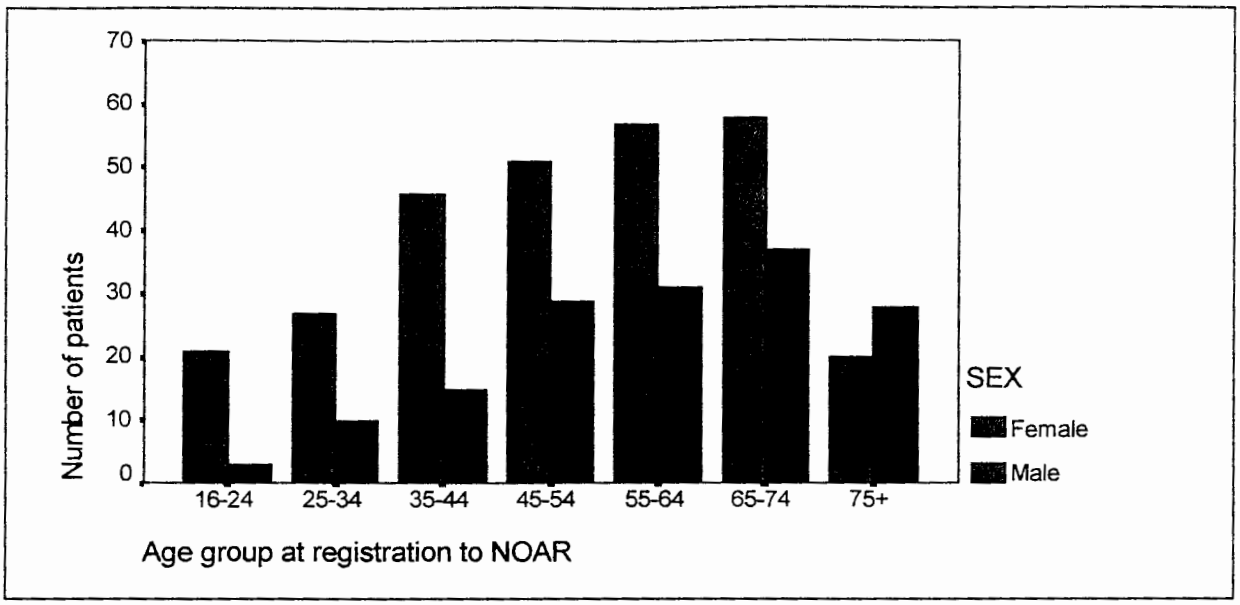
The mean age of the study population was 55 years (sd=16.0) with the average age for males [61 years (sd=14.8)] exceeding the average age for females [52 years (sd=15.9)]. The number of females diagnosed exceeded the number of males in all age categories except the elderly (>75 years). The distribution for the age at onset of the study population, depicted in figure 1, reflected that of a previous study[11]. Approximately 50% of the study population were classified as having RA.

Table 1: Summary of socio-demographic characteristics of study cohort at baseline [Mean(SD),%].

SOCIO-DEMOGRAPHICS	Study Population (n=344)
Delay in presentation to NOAR	164.5 days
HAQ score (0-3)	0.975 (0.771)
Age (yrs)	55 (16.0)
16 - 64 (%)	65.4%
≥ 65 (%)	34.6%
% female	64.0%
% Caucasian	100.0%
% working[a]	39.0%
% smoking now	25.6%
% smoked past	30.5%
% Rheumatoid factor positive[b]	34.4%
% Classified as having RA	49.7%
Social Class[c]	
I (%)	1.7%
II (%)	22.4%
IIIM (%)	17.7%
IIIN (%)	20.3%
IV (%)	19.8%
V (%)	3.8%

[a] 1.8% of data missing. [b] 11.9% of data missing. [c] 14.2% of data missing

Figure 1: Age distribution of 433 people who enrolled on the NOAR project 1990 / 1991 split by gender.



No statistically significant differences in the socio-demographic characteristics of the two registration years (1990 and 1991), and the two completion groups (five years and part completion of five years) existed at the 5% level.

Five year cost analysis:

Secondary health service care costs:

Outpatient costs: Over the five year study period, 77% of the study cohort visited outpatients at least once. The percentage of people visiting outpatients in any one year decreased over time from 67% to just 35%. Table 2 shows the median number of outpatient visits per person per year to equal either 0 or 1. Members of the study cohort who were more disabled at registration (i.e. HAQ score $\geq$ 1.0) were found to encounter significantly more outpatient visits over the five year study period than those who were less disabled (i.e. HAQ score < 1.0) [$p<0.0001$, Mann-Whitney Test]. No statistically significant differences were obtained between the age groups (i.e. age < 65 years and age $\geq$ 65 years) [$p=0.1635$].

Table 2: Median (per person) outpatient visits, inpatient stays, total secondary health service care and second line drug (including routine laboratory tests) costs for the whole study cohort.

SECONDARY HEALTH SERVICE CARE					
OUTPATIENTS		INPATIENTS		TOTAL	SECOND LINE DRUGS
Median No. of outpatient	Median cost per	Median length of	Median cost per person	Median cost per person	Median cost per person

	visits	person	hospital stay			
1st Year	1 (0-5)	£52 (0-138) [47 (47)]	13 (0-20)	£0 (0-3,079) [292 (131)]	£52 (0-3,133) [339 (1,329)]	£0 (0-256) [58 (86)]
2nd Year	0 (0-4)	£0 (0-86) [24 (32)]	9 (0-13)	£0 (0-1,351) [105 (549)]	£0 (0-1,490) [129 (559)]	£0 (0-301) [66 (102)]
3rd Year	0 (0-4)	£0 (0-86) [22 (34)]	9 (0-17)	£0 (0-3,025) [177 (727)]	£0 (0-3,154) [199 (738)]	£0 (0-323) [75 (165)]
4th Year	0 (0-4)	£0 (0-93) [20 (36)]	8 (0-10)	£0 (0-2,485) [166 (810)]	£0 (0-2,520) [186 (831)]	£0 (0-407) [79 (160)]
5th Year	0 (0-4)	£0 (0-86) [16 (27)]	4 (0-11)	£0 (0-1,226) [111 (683)]	£0 (0-1,291) [127 (692)]	£0 (0-349) [53 (100)]
Total	3 (0-20)	86 (0-451) [124 (132)]	9 (0-17)	£0 (0-7,510) [813 (2,590)]	£95 (0-7,732) [937 (2,662)]	£21 (0-1,439) [313 (494)]

Costs expressed in 1990/1 UK£. (2.5th to 97.5th centiles). [Mean (Standard deviation)].

The distribution of outpatient costs were positively skewed for all five years of the study, with median costs ranging from £0 (2.5th centile = £0; 97.5th centile = £86) to £52 (2.5th centile = £0; 97.5th centile = £138) per person per annum (Table 2). Overall, the median (per person) outpatient cost was calculated to be £86 (2.5th centile = £0; 97.5th centile = £451) for the total five years.

Inpatient stays: Over the five year study period, 21% of the study cohort were admitted to hospital at least once. Overall, the median length of a hospital stay for these people was 9 days (2.5th centile = 0; 97.5th centile = 17) (Table 2). Those people who were aged less than 65 years and had a HAQ score below 1.0 at registration to NOAR, were found to incur a significantly shorter length of hospital stay [$p<0.001$; Mann-Whitney test].

The median (per person) inpatient cost was calculated to be £0 for all five years of the study, due to only a minority of the study cohort being admitted to hospital (Table 2). The majority of the inpatient costs recorded, due to a persons' arthritis, were incurred by the Rheumatology department (£217,127) with a small proportion incurred by the Orthopaedic department (£56,815).

Overall, secondary health service care: Inpatient and outpatient costs incurred over the five year period were found to have a positive association (Spearman's rank correlation coefficient,

r_s = 0.499; p<0.0001); i.e. those people who incurred high inpatient costs tended to also incur higher outpatient costs and vice versa.

Over the five year study period, 78% of the study population incurred secondary health service care costs. The median (per person) cost for the five year period was £95 (2.5th centile = £0; 97.5th centile = £7,732) (Table 2). A statistically significant cost difference was found between the two HAQ score groups [p<0.0001; Mann-Whitney test], suggesting people with more disability at registration to NOAR incurred higher secondary health service care costs. No statistically significant cost difference existed between the two age categories [p=0.5841; Mann-Whitney test].

Second line drugs and toxicity management:

Twenty-four percent of the study cohort had been prescribed second line drugs prior to registration. During the five year study period, the percentage of the study cohort prescribed second line drugs ranged from 34% in the fifth year to 44% in the first and second years. Almost two-thirds of the study population who were prescribed second line drugs in their first year were prescribed Sulphasalazine but by the fifth year this proportion had been reduced to one-third of the cohort. The most expensive second line drug was found to be Cyclosporin, costing £6,833 (for 6 people) over the five year study period.

Overall, the median (per person) five year cost of second line drugs was calculated to be £21 (2.5th centile = £0; 97.5th centile = £1,439) (Table 2). Sixteen percent of the total five year second line drug costs, was spent on the routine laboratory tests designed to manage the toxicity of the different drugs. Statistically significant differences resulted between the cost of second line drugs (including routine laboratory tests) for the two HAQ score categories [p<0.0001, Mann-Whitney test]. No significant differences were obtained between the age categories [p=0.7790; Mann-Whitney test].

Total costs - Secondary care and Second line drug costs:

Secondary health service care and second line costs incurred over the five year period were found to have a positive association (Spearman's rank correlation coefficient, r_s = 0.6737;

p<0.0001); i.e. those people who incurred high secondary health service care costs tended to also incur higher second line drug costs and vice versa.

Twenty-one percent of the study population neither visited hospital nor were prescribed second line drugs during the 5 year study period. The percentage of the study population who incurred secondary care and/or second line drug costs declined from 69% in the first year to 46% in the fifth year. The total cost for the first five years of secondary care and second line drugs (including routine laboratory tests) was estimated to be approximately £421,286, equivalent to a median (per person) cost of £195 (2.5th centile = £0; 97.5th centile = £8,804). Overall, inpatient costs accounted for 65% of the total five year costs, second line drug costs (including routine laboratory tests) 25%, and outpatient costs 10%.

Figure 2: Total 5 year secondary care and second line drug costs.

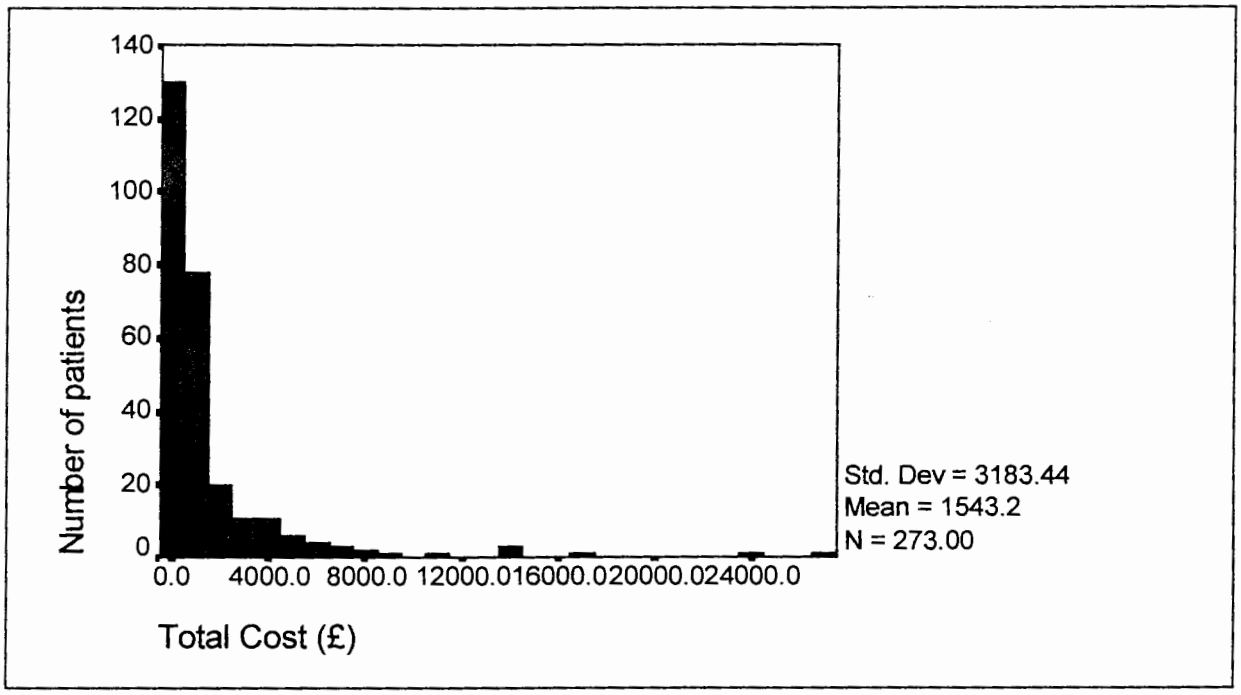


Figure 2 presents the total 5 year secondary care and second line drug costs for all of the 300 people in the study who completed 5 years of follow-up. The 75th percentile (£1,377) was chosen as the cut-off point between low and high cost [5]. Out of these 300 people, 57 people (21%) incurred 'no secondary care and second line drug costs', 181 people (60%) incurred 'low costs' and the remaining 62 people (21%) incurred 'high costs'. The socio-demographic characteristics of these three groups of people are presented in Table 3. Overall, the people in

the 'high cost' group tended to have higher HAQ scores and the presence of rheumatoid factor[6] at registration, and were lower in age than those in the 'zero cost' group.

Table 3: Characteristics of the study population with 'zero cost' versus 'low cost' (≤£1,377) and 'high cost' (>£1,377).

	Zero cost (n = 57)		Low cost (n = 181)		High cost (n = 62)		
	Mean (s.d.)	**Median**	**Mean (s.d.)**	**Median**	**Mean (s.d.)**	**Median**	**P-value *(Krushall -Wallis)***
HAQ score at onset	0.77 (0.69)	0.63	0.90 (0.75)	0.75	1.44 (0.74)	1.50	*p<0.0000*
HAQ score at 5 yrs	0.67 (0.67)	0.50	0.85 (0.71)	0.63	1.67 (0.81)	1.75	*p<0.0000*
Age at onset	59 (15.58)	61	54 (16.91)	55	56 (13.01)	55	*p=0.0297*
% smoke now	26%		28%		24%		
% smoke past	39%		44%		44%		
% Rfactor positive	11%		30%		57%		
% Female	66%		62%		68%		

Only includes the 300 members of the cohort who completed 5 years follow-up. [a]Significant 5% level ($p<0.05$).

Regression analysis:

A logistic regression model was constructed for 'low cost' versus 'high cost' using the forward stepwise method[10]. The 57 people who incurred 'no costs' were excluded from this part of the analysis. In line with the above findings, the HAQ score at registration to NOAR (entered as a categorical variable) was found to be one of the main predictor variables. The presence of rheumatoid factor (RFactor) at registration was found to be the other main predictor variable in the model (Table 4)

Table 4: Logistic Regression Model

Variable	B	S.E.	Exp(B)	95% CI
RFACTOR, η_1	.9606	.3374	2.6133	1.30 to 5.06
HAQBAND1, η_2	1.7215	.3551	5.5926	2.79 to 11.2
Constant, η_0	-2.4329	.3340		

[6] Rheumatoid factor is a form of antibody to type II collagen. It is thought that these antibodies are evidence of auto-immune responses that bring about RA, and for this reason are an important diagnostic variable[12].

The parameter estimate for the cost associated with HAQ score category at registration to NOAR, was 1.7215 (i.e. the log odds ratio), which converts to an odds ratio of 5.5926 (exp(1.7215)) with a 95% confidence interval from 2.79 to 11.2. This indicated that the probability of incurring secondary health service care and second line drug costs is higher for those people with a HAQ score of 1.0 or greater at registration.

Similarly, the odds ratio for the cost associated with the presence of rheumatoid factor at registration, is exp(0.9606) = 2.6133 with a 95% confidence interval from 1.30 to 5.06. Again, this indicates that the probability of incurring secondary health service care and second line drug costs is higher for those people with rheumatoid factor present at registration.

Table 5 shows the estimated probability and observed proportion of people with inflammatory arthritis incurring high costs for each of the four possible combinations of HAQ score and rheumatoid factor categories. The agreement between predicted and observed is extremely good. The data shows that high costs over the first five years are most common when positive rheumatoid factor and HAQ score ≥ 1.0 are both recorded at registration to NOAR.

Table 5: Predicted probability of cost (P_{hcost}) and observed proportions.

RFactor (X_1)	HAQ score (X_2)	L	P_{hcost}	Observed proportion
-ve (0)	<1.0 (0)	-2.4329	0.08	0.06
-ve (0)	≥1.0 (1)	-1.4723	0.19	0.23
+ve (1)	<1.0 (0)	-0.7114	0.33	0.36
+ve (1)	≥1.0 (1)	0.2492	0.56	0.53

$L = \text{logit}(P_{hcost}) = \log(P_{hcost}/(1-P_{hcost})) = \eta_0 + \eta_1 X_1 + \eta_2 X_2$

P_{hcost} = Probability of 'high cost' = exp(L)/[1+exp(L)]

Sensitivity Analysis:

The uncertain parameters in the analyses outlined above, were the second line drug costs, which omitted the professional fees, overheads and the management of side effects in problem cases, and the secondary care costs which were based on imprecise hospital prices rather than actual costs. By reworking the calculations, the lower extreme for the total five year cost of

the whole study population (reducing inpatient and outpatient unit costs by 10%) was £389,699 and the upper extreme (increasing inpatient and outpatient unit costs by 10%, and second line drugs' unit costs by 20%) was £470,518.

Discussion:

Based on the NOAR data it can be estimated that there are approximately 22,700 new cases of inflammatory arthritis per year in the United Kingdom[6]. Using this figure, and assuming 20% of all people with early inflammatory arthritis incur 'no costs', the total five year secondary care and second line drug costs (including routine laboratory tests) for these new cases can be estimated as approximately £29.4 million (1990/91 prices) or an average cost of £5.9 million per year. This can be broken down as approximately £19.1 million (65%) on inpatient care; £2.9 million (10%) on outpatient care; and £7.4 million (25%) on second line drugs including routine laboratory tests.

The largest component of the medical costs considered by this study were inpatient stay costs, despite only being incurred by a small proportion of the study cohort. In fact, the 21% of the study cohort who incurred inpatient costs were responsible for 80% of the total five year costs incurred by the cohort as a whole. Such findings were consistent with other studies' results[1,4,13-18]. Approximately a fifth of the study cohort incurred 'no costs', a result not recorded by other studies. However, this was to be expected as the NOAR is a community-based register and people are referred from their GP as well as from the hospital-based clinics.

The results of the multiple logistic regression model agreed partly with the findings of van Jaarsveld et al (1998)[5], who found the probability of high costs increased with functional disability (measured by the HAQ) but decreased with age. It is possible that the significance of the HAQ score recorded at registration and the presence of rheumatoid factor on cost, reflects the stage of a person's inflammatory arthritis at diagnosis and/or any co-morbidities a person may be suffering from. It is reported that in most cases there is a steady trend towards increasing functional disability over the lifetime of the disease while for a small proportion of people the move towards disablement is much more rapid[12]. It seems reasonable to assume that this small proportion of people incurred the higher costs in the above analysis.

The results of this study present a conservative picture of the secondary care and second line drug costs as outpatient visits of the study cohort to other health professionals such as data on physiotherapists, nurse practitioners, chiropodists and occupational therapists were not available for inclusion in the costing analysis. Using data from McIntosh 1996[4], the inclusion of such costs could increase the costs of outpatient visits by as much as 60%. Other costs such as hand and feet x-rays which are usually taken annually and the management of side effects in problem situations were also omitted from the analysis.

The cost estimates calculated in this study rely on inpatient and outpatient charges provided by the local provider rather than the actual observed cost. It is usual for the average hospital charges to exceed the actual costs to allow for expansion and the replacement of equipment and facilities over time which become increasingly expensive due to inflation and technological improvements[19]. As such costs also vary from provider to provider they may not adequately reflect resource use. However, this issue was addressed in the sensitivity analysis.

Conclusion:

By enabling potentially 'high' cost patients with inflammatory arthritis to be identified at the time of diagnosis, the above findings may be used to assist the decision-making process by leading to more advanced planning and allocation of resources. In addition, it may be possible to use data from this study to investigate the cost-consequences of alternative treatment regimes in the future.

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References

1. Meenan RF, Yelin EH, Henke CJ, Curtis DL, Epstein WV. The costs of rheumatoid arthritis. A patient-oriented study of chronic disease costs. Arthritis Rheum 1978; 21:827-833.

2. Stone CE. The lifetime economic costs of rheumatoid-arthritis. J Rheumatol 1984; 11:819-827.

3. Jonsson B, Rehnberg G C, Borgquist L, Larsson SE. Locomotion status and costs in destructive Rheumatoid Arthritis - A comprehensive study of 82 patients from a population of 13,000. Acta Orthopaedica Scandinavica 1992; 63:207-212.

4. McIntosh E. The cost of rheumatoid-arthritis. Br J Rheumatol 1996; 35:781-790.

5. van Jaarsveld CHM, Jacobs JWG, Schrijvers AJP, Heurkens AHM, Haanen HCM, Bijlsma JWJ. Direct cost of rheumatoid arthritis during the first six years: A cost-of-illness study. Br J Rheumatol 1998; 37:837-847.

6. Symmons DPM, Barrett EM, Bankhead CR, Scott DGI, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: Results from the Norfolk arthritis register. Br J Rheumatol 1994; 33:735-739.

7. Cooper NJ. Economic burden of rheumatoid arthritis: A systematic review. Unpublished.

8 van Gestel AM, Haagsma CJ, Furst DE, et al: Treatment of early rheumatoid arthritis patients with slow-acting anti-rheumatic drugs (SAARDs). in Woolf AD, Van Riel PL (eds): Early rheumatoid arthritis. London, Baillere's Tindall, 1997, pp 65-82.

9. Netten A, Dennet J. Unit costs of health and social care. 1997; (Abstract)

10. Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.

11. Brewerton D. All about arthritis: Past, present and future. Cambridge, Massachusetts: Harvard University Press, 1992; 136-142.

12. Newman S, Fitzpatrick R, Revenson TA, et al. Understanding rheumatoid arthritis. London: Routledge, 1996.

13. Clarke AE, Zowall H, Levinton C, et al. The medical costs incurred by Canadian patients with rheumatoid-arthritis - A 12 year study. J Rheumatol 1997; 24:1051-1060.

14. Liang MH, Larson M, Thompson M, et al. Costs and outcomes in rheumatoid arthritis and osteoarthritis. Arthritis Rheumat 1984; 27:522-529.

15. Jacobs J, Keyserling JA, Britton M, Morgan GJ, Jr., Wilkenfeld J, Hutchings HC. The total cost of care and the use of pharmaceuticals in the management of rheumatoid arthritis: the Medi-Cal program. J Clin Epidemiol 1988; 41:215-223.

16. Lubeck DP, Spitz PW, Fries JF, Wolfe F, Mitchell DM, Roth SH. A multicenter study of annual health service utilization and costs in rheumatoid arthritis. Arthritis Rheumat 1986; 29:488-493.

17. Spitz PW. The medical, personal, and social costs of rheumatoid-arthritis. Nursing clinics of North America 1984; 19:575-582.

18. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. J Rheumatol 1997; 24:719-725.

19. Finkler SA. The distinction between cost and charges. Ann Intern Med 1982; 96:102-109.